Urodynamics, Neurourology and Pelvic Floor Dysfunctions

Alessandro Giammò
Antonella Biroli *Editors*

Chronic Pelvic Pain and Pelvic Dysfunctions

Assessment and Multidisciplinary Approach

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Urodynamics, Neurourology and Pelvic Floor Dysfunctions

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Foreword

I thank the editors, Antonella Biroli and Alessandro Giammò, for entrusting me with the task of this presentation. The publication of a new comprehensive textbook on “Pelvic Pain” is for me an exciting opportunity to reiterate some concepts in the field of functional urology.

The cure of a disease implies the identification of its etiology, a steady axiom in doctors’ and researchers’ mentality since the dawn of medicine. The aim of physiopathology, instead, is an attempt to understand the mechanisms that lead to the condition of disease.

Therefore, etiology and pathophysiology do not coincide: etiology identifies the cause of a renal colic in a ureteral calculus; the pathophysiology explains the pathogenic mechanisms by which the typical pain of a renal colic is determined.

This concept is particularly suitable in the context of an organic disease; it is less suitable in the functional field, in particular when the main problem that leads the patient to the doctor is pain; in functional diseases, an obvious etiological origin cannot be identified in most cases. Therefore, in these conditions, therapy cannot be applied to the cause of the problem, but it should be adapted on the underlining definition of the physiopathological condition. This process requires the knowledge of the pathogenetic mechanism that determines a specific dysfunctional condition, independently from its cause.

In most cases, in the clinical practice of functional urology we do not know neither the etiology nor the pathogenetic mechanism according to which a specific dysfunctional condition has developed.

I have been trying to spread a new concept in the field of functional urology for many years. It has the ambition to outline a different clinical approach to the various dysfunctional pathologies. I defined this new approach "the third way" and it is applicable to various pathological conditions in functional urology, such as overactive bladder, female stress incontinence, and nonobstructive urinary retention (i.e., in the absence of an organic or functional obstruction).

I am convinced that the same approach can be employed to the management of chronic pelvic pain, the topic of this book.

I will, therefore, try to explain what I mean with "Third Way."

With regard to the various dysfunctional urological pathologies, there is plenty of clinical evidence, on which we have built well-defined Guidelines and we have proposed high-grade Recommendations, both in the diagnostic and in the

therapeutic field. The resulting management algorithms are built according to the different pathologies, but they all have a characteristic in common: the distinction of the clinical path in two phases.

The first phase is based on the clinical definition of the problem, and therefore on the symptoms that allow to formulate a "presumptive diagnosis." On the basis of this presumptive diagnosis, it is possible to prescribe a therapy, provided that it is not invasive. When this path leads to an apparently insurmountable wall (i.e., the patient does not gain any benefit from therapy), we go back and undertake the second route (the second phase). It is based on a detailed definition of the dysfunctional condition, with the aim to reach at a "definite diagnosis." At this point, the algorithms list a series of possible therapeutic strategies, including the invasive ones, without precisely indicating to which of the different therapies and in which sequential order we have to rely on.

And here comes the "Third Way."

The "Third Way" is indicated by the "physiopathological interpretation" and allows to choose the most appropriate therapy.

The pathophysiological interpretation of overactive bladder, stress incontinence, detrusor acontractility, as well as of that clinical and dysfunctional conditions known as "Pelvic Pain Syndrome" or "Bladder Pain Syndrome" (in the context of Chronic Pelvic Pain) is still based on apparently well-established theories and hypotheses, but they are far from being conclusively defined. It is interesting to underline that the term Pelvic Pain Syndrome is correctly proposed when an etiology cannot be identified in a chronic pelvic pain nor the physiopathological process underlying is clear.

Thus, the "clinical sense" comes into play as an element that we have partially lost. The "clinical sense" can lead us to hypothesize the most probable underlying physiopathological condition of a specific clinical syndrome; on the basis of this individualized interpretation, we will be able to prescribe the most appropriate therapy.

This book, edited by Antonella and Alessandro, with an impressive number of renowned contributors, deals with the topic of pelvic pain with particular attention to the diagnosis and treatment of this disorder. The pelvic pain syndrome does not recognize a specific etiology; pathogenesis is also poorly defined. It follows that therapy most of the time is based on the pathophysiological interpretation of the problem and on clinical common sense.

I conclude this brief presentation with the aphorisms of two great thinkers of the last century, Norberto Bobbio and Karl Popper.

The first claimed that "... today, the duty of men of culture is more than ever to sow doubts not to harvest certainties."

The second one said, "Whenever a theory seems the only possible one, consider it as a sign that you have not understood neither the theory nor the problem that you intended to solve."

However, it is also true that "Hypotheses are nets: only he who casts will catch " (Novalis, philosopher).

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Preface

It is our pleasure to introduce the present volume under the auspices of the Italian Society of Urodynamics. A distinguished, interdisciplinary faculty has made the valuable effort to clarify crucial clinical aspects of Chronic Pelvic Pain and Pelvic Dysfunctions. Authors shed lights on the relevant pathophysiology of such a disabling condition, offering updated and practical suggestions for its management.

Typically in our series, but particularly in this case, multidisciplinary and multiprofessional perspective represents the key element of the volume: the text will find the interest of urologists, gynecologists, colorectal surgeons, gastroenterologists, as well as physicians specialized in physical medicine and rehabilitation, neurology, anesthesiology, rheumatology, and psychiatry. Moreover, other team members could benefit from its content: nursing, physiotherapy, occupational therapy, kinesiology, clinical nutrition, psychology, pharmacy, and social workers.

Another precious piece of knowledge adds to the series of Springer volumes edited by the Italian Society of Urodynamics.

Enjoy the reading.

Milan, Italy — Marco Soligo

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Part I

The Nervous System and Pain

Introduction to Pain

1

Nicola Luxardo

The International Association Study of Pain (IASP) identifies "pain" as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [1]. This definition, first published in Pain Journal in 1979, comes from the works made by Harold Merskey almost 15 years before, that is in 1964.

1.1 Anatomy of Pain Pathways

1. Primary afferent neuron (PAN): begins from the periphery and reaches the spinal cord where it stops in the superficial segments at the synapse with secondary neuron and interneurons. The PAN is represented by a T cell with the body located in the spinal ganglion or in the Gasser ganglion.
2. Secondary neuron can lead the electrical signal throughout the paleo- or neospinothalamic pathway. In the first case there are many synapses before reaching the medial thalamus; in the second case, it arrives immediately to the lateral part of thalamus.
3. Perception and processing take place in the cerebral cortex where pain signal becomes conscious. A pain center does not exist because the entire brain is involved: insula cortex, cingulate cortex, and prefrontal cortex process emotive and cognitive components of pain, instead the somatosensory cortex elaborates sensory components, in particular the localization and the intensity.

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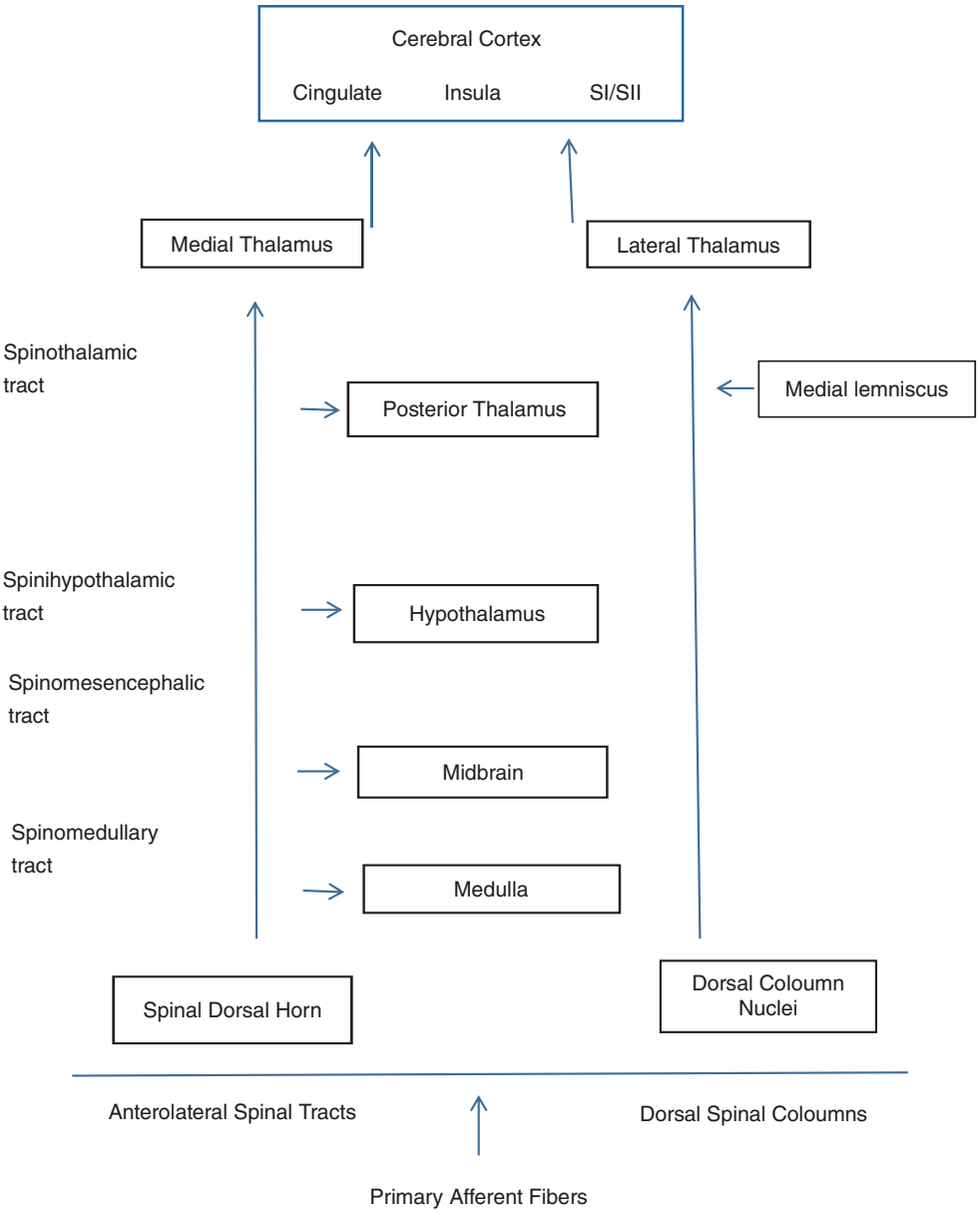

Fig. 1.1 Pain network

4. Descending fibers from the cortex to periaqueductal gray and raphe magnus nucleus reach the spinal cord's interneurons and can modulate the input of the pain signal inside the cenral nervous system [2] (Fig. 1.1).

1.2 Physiology of Pain

Physiology of pain includes:

1. Transmission
2. Modulation
3. Perception and processing
4. Modulation

Transduction occurs at the end of peripheral nerves where pain receptors called "nociceptors" are located. These corpuscles at the primary afferent neuron level are able to convert a mechanical, heating, or chemical stimulus to an electrical signal when the body experience is an injury or an inflammation.

In normal conditions, nociceptors are activated by high-intensity stimuli.

Transmission is the path from the nociceptors to the cerebral cortex through the peripheral nervous system (PNS) and CNS.

Perception and processing include many brain areas that determine location and intensity of pain, add emotional and cognitive component, activate the memory, and consequently influence the behavior.

Modulation: Pain is not transmitted always with the same intensity, but can be modulated in excess or defect by cortical and subcortical structure. These areas are activated by particular situations like stress or placebo in order to face dangerous events for the life.

The most important target is the synapse between primary and secondary afferent neurons; at this level we can act with opioid therapy or with non-pharmacological approach such as TENS or spinal cord stimulation [2].

1.3 Classification of Pain

According to pathophysiology pain can be classified as:

1. Nociceptive pain: caused by physiologic activation of pain receptors; has natural physiologic transduction; can be local and referred pain, is a normal physiological sensation; has a good answer to analgesic therapy [3].
2. Neuropathic pain: caused by an injury or dysfunction in central and peripheral nervous system [4]; is inside a neuroanatomical field; characterized by new and strange sensations, strange and new feelings.

3. Nociplastic pain: arises in the CNS, caused by an imbalance inside the regulatory system of the nociceptive pathway [5].

According to time pain can be classified as:

1. Acute pain: biological function of protection; time limited; single cause.
2. Chronic pain: long lasting; useless; multiple causes; self-sustaining.

In the past chronic pain was considered the symptom of a chronic disease linked to a temporal parameter, it is now considered a disease of its own on the basis of a pathophysiological criterion no longer resolvable. It can be tied to three mechanisms:

1. Mechanism of injury and pain are similar or the same.
2. Pain has its own mechanism in addition to those of the disease.
3. Pain has own mechanism completely different from those that caused the disease.

The transition from acute to chronic pain is a process not still clarified, but many elements can be involved as peripheral inflammation, neuropathic factors, peripheral and central sensitization, psychological and social factors.

Continuous stimulation modifies the nervous system through the mechanism of plasticity with three possible consequences:

- Peripheral sensitization
- Central sensitization
- Cortical reorganization

The nervous system as a whole becomes much more active [6]. Functional magnetic resonance imaging studies have shown that the brain of a person suffering from chronic pain is different from that of an asymptomatic subject: in particular, in the first case the images show hyper neuronal activity.

In acute pain, nociceptors, pain receptors located on the end of peripheral nerves, are activated when the body experiences an injury or an inflammation. The nerves in the periphery send pain signals through the dorsal root ganglion, to the spinal cord and central nervous system. When pain is acute, signaling typically stops once the cause of pain is resolved [7].

However when pain becomes chronic and lasts more than 3 months, repeated stimulations of sensory nerves determine changes to the pathway of pain signals leading to a pathophysiological self-regenerating mechanism where nervous system is sensitized and the perception of pain becomes higher.

Both peripheral and central nervous systems can be sensitized to pain signals in response to injury or inflammation and nociceptors in periphery can increase their sensitivity to painful stimuli; the process is called peripheral sensitization. These sensitized nociceptors consequently send additional pain signals to the central nervous system which can lead to the overstimulation of CNS. This results in a central

sensitization which increases the perception of pain. In this way, central sensitization leads to the perpetuation of pain.

Sensitization starts at the molecular level [8]. In response to an injury or inflammation cells of the site of pain release variety of biochemical mediators including neurotrophin NGF (nerve growth factor), the citochina TNF (tumor necrosis factor), the interleukin IL-1beta, IL-6 (interleukin), and PG E2 (prostaglandin). These mediators bind nociceptors in periphery leading to sensitization on the pain pathway. When the cause of pain continues over time, the persistent activation of the pain pathway leads to increase in the synthesis of glutamate, neuropeptides such as substance P and CGRP, and BDNF [9–12].

Substance P and CGRP enhance the sensitization of the sensory nerves in the periphery. In the CNS, all four of these mediators can be released by the primary afferent neurons subsequently binding in the receptors in the dorsal horn of the spinal cord contributing to the activation of the principal intracells pathway and initiate the central sensitization.

NGF plays a key role in the amplification of the pain signal by sensitizing neurons into pain pathway and causing an overproduction of other pain mediators. It is found throughout the body that levels of NGF increase in respond to injuries or conditions associated with pain. In presence with some conditions associated with chronic pain like osteoarthritis, rheumatoid arthritis, gout, or chronic low back pain, there is a continuous overproduction of NGF. As a result, more NGF is available to bind to peripheral sensory nerves increasing the number of pain signals that trouble from the periphery to the CNS [13–15].

This contributes to the sensitization of the nerves in both peripheral and central nervous system amplifying and perpetuating chronic pain.

The relationship between the periphery and the central nervous system provides a key insight on the chronic pain.

Peripheral sensitization (PNS), central sensitization (CNS), and heightened perception of pain (NEUROMATRIX) are segments of the same phenomenon.

1.4 Conclusion

Around the world one-fifth of people suffer from moderate to severe chronic pain. Chronic pain has a significant negative impact on the quality of the patient's life and in particular can produce sleepiness, decreased activity, and mood changes such as depression, anxiety, anger, and fatigue and through the hypothalamus-hypophysis-adrenal gland axis can cause chronic stress.

Chronic pain therefore changes the way of living: the affected person adapts to the new situation and the pain becomes the center of existence causing avoidance behaviors, social withdrawal, and catastrophism. It is therefore an individual complexity, characterized by a multifactorial experience and a successful therapeutic strategy must include addressing the emotional, cognitive, social aspects and not only somatic pain.

The first phase of treatment must necessarily be the breakdown of pain into its constituent elements, observing, asking, listening, and only after visiting the patient.

The goal is to diagnose pain generator and underlying physiopathological mechanisms, recognize the emotional and cognitive elements, to know the person in front of us, behavior, the social and family environment.

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Neurophysiology of Visceral Pain

2

Paolo Costa

2.1 Introduction

Visceral pain, the pain that originates from the thoracic, abdominal, or pelvic organs, is the most common cause of pain and represents a diffuse social problem because of the relevant impact on quality of life [1–10]. Some epidemiological data are shown in Table 2.1.

Although visceral pain has often been interpreted in light of existing knowledge about somatic pain, there are important differences to be emphasized. According to Cervero [11] the five main clinical features that make visceral pain unique are summarized in the following Table 2.2:

So far, much of what we know about the mechanisms of pain derives from studies on somatic pain and not from visceral pain, which can be the cause of clinical and methodological errors [12]. Somatic and visceral pain have many similarities but also relevant differences in neurophysiological mechanisms, clinical presentation, and psychological issues. The knowledge of the different pathophysiological mechanisms influences the type of treatment that can be unrelated to the etiological cause: in this sense pain must be seen as a syndrome rather than a symptom [12, 13]. A precise knowledge of neurophysiological mechanisms of visceral pain may be to better define the syndromes and to target therapy.

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Table 2.1 Epidemiology of visceral pain

Condition	Epidemiology	Reference
Chest pain	Every year 4% of general population consult the general practitioner for chest pain	[1]
	Large majority of chest pain (20.4%) is of musculoskeletal origin, followed by reflux esophagitis (13.4%), and costochondritis (13.1%). Angina pectoris is the primary diagnosis in 10.3%, possible myocardial infarction in 1.5%	[2]
Gastrointestinal pain	Symptoms suggestive of irritable bowel syndrome (IBS) are reported from 10% and 20% of the general adult population in the United States. Women are diagnosed more often than men (2:1)	[3]
	There is a high comorbidity of IBS with non-gastrointestinal (GI) pain disorders as fibromyalgia and affective disorders. 65% of women with IBS present symptoms attributable to chronic pelvic pain (CPP) (35%), and urinary frequency and urgency (65%) (5)	[4]
Chronic pelvic pain (CPP)	1 woman of 7 in the USA is affected by CPP	[5]
	A third is due to endometriosis, a third due to adhesions, and a third have no obvious pathology; probably the first two are estimated and a central neurological cause is likely	[6]
Chronic bladder pain (CBP)	1.3% of men and 2.6% of women referrer ongoing pain associated with bladder function that had been lasting three or more months Documented interstitial cystitis affects 0.5% of the population with a female predominance of 10:1	[7]
Prostate pain syndrome (Pps)	Chronic prostatitis without demonstrable infection affects six million men in the USA	[8]
Scrotal pain	The incidence of post-vasectomy pain which is between 15% and 19%	[6]
Vulvar pain syndrome or Vulvodynia	Vulvodynia is common between the ages of 20 and 60 and may reach 15%. It is frequently associated with pain with first tampon use, CBP and functional bowel disorders	[9] [10]

Table 2.2 Clinical characteristics of visceral pain

1. Not evoked from all viscera 2. Not linked to visceral injury	Related to the functional characteristics of the peripheral receptors that innervate different visceral structures; Many viscera receive innervation by not strictly speaking sensory receptor because their activation does not evoke conscious perception
3. Referred to other locations 4. Diffuse and poorly localized 5. Associated to exaggerated motor and autonomic reflexes	Related to the central organization of visceral nociceptive mechanisms, in particular by the lack of a separate visceral sensory pathway in the spinal cord and brain and to the very low proportion of visceral afferent fibers compared to those of somatic origin

2.2 Clinical Presentation of Visceral Pain

There are several phenomena associated with visceral pain and it can present in a variety of forms.

2.2.1 True Visceral Pain

Visceral pain is generally diffuse and poorly localized. This can be explained in light of the low density of visceral innervation and of the diffuse divergence of the input within the central nervous system [14]. It usually has a temporal evolution and can be difficult to identify in its early stages [14, 15].

Symptoms can be very mild, as a poorly defined sense of discomfort or to be associated with autonomic phenomena; generally emotional reactions (anxiety, sometimes sense of impending death) occur.

2.2.2 Referred Pain and Hyperalgesia (Viscero-somatic Convergence)

The visceral pain can present as a pain at somatic sites and this phenomenon is known as "referred pain" [16]. This is a consequence of viscero-somatic convergence in the spinal cord from the visceral organ and somatic areas at the same spinal sensory neurons [15–19]. The scarcity of visceral afferent fibers well explains the viscero-somatic convergence: the percentage of fibers afferent to the spinal cord would be less than 10% of the somatic ones [12]. Moreover, visceral afferent terminals have a more widespread distribution in the spinal cord than somatic ones [20]. This pain is described as deep somatic pain, sharper, is better localized than true visceral pain and not accompanied with any sympathetic or emotional reactions. Referred pain can be considered as a misinterpretation of pain localization by higher brain center, due to the convergence of visceral and somatic afferent fibers onto the same spinal sensory neurons [14, 17, 21]. Referred pain is frequently associated with hyperalgesia (i.e., increased sensitivity to painful stimuli): this phenomenon is probably an effect of central sensitization, involving viscero-somatic convergent neurons ("convergence-facilitation") [15].

The term "referred pain with hyperalgesia (i.e., increased sensitivity to painful stimuli)" defines the association of referred pain and hyperalgesia.

2.2.3 Visceral Hyperalgesia

Visceral hyperalgesia is an increased sensitivity of an internal organ such that even normal stimuli may produce pain from that organ [22].

Visceral hyperalgesia is thought to be the consequence of visceral inflammation that induces central or peripheral sensitization [23].

2.2.4 Viscero-visceral Hyperalgesia

This is an augmentation of pain symptoms due to the sensory interaction between two different internal organs that share at least part of their afferent circuitry [24, 25]. Viscero-visceral hyperalgesia appears to be produced by sensitization processes involving viscero-visceral convergent neurons in the CNS [14].

In chronic visceral pain from viscero-visceral hyperalgesia, treatment of one visceral condition may effectively relieve symptoms from the other [26, 27].

2.3 Pathophysiology of Visceral Pain

2.3.1 Visceral Nociceptors and the Primary Afferent

All the thoracic and abdominal have a dual afferent innervation, classically referred to as sympathetic and parasympathetic, but more appropriately designated by nerve name (for example, hypogastric nerve, pelvic nerve). These afferences provide reflex control of visceral functions (cardiopulmonary, gastrointestinal, genitourinary) by conveying information from the viscera to the CNS. The majority of such information does not reach the conscious level [28]. Receptors (the terminals of primary visceral afferent neurons) are located in all layers of a hollow organ [23]. Visceral afferent neuron terminals are activated by luminal and local chemical stimuli and by mechanical (usually distending) stimuli [28]: in fact, visceral receptors usually respond to multiple modalities of stimulation (polymodal receptors) [22].

Nociception is initiated by activation of visceral receptors, and if the stimulus is sufficiently strong, it is transduced into a pain signal and transmitted to the dorsal horn of the spinal cord [29]. In the viscera, Aδ- and C-fibers respond to noxious stimuli, which may be mechanical, thermal, or chemical [30]. Aδ-fibers are small in diameter and thinly myelinated fibers and transmit stimuli faster than the nonmyelinated C-fibers.

2.3.2 Peripheral Sensitization

Following repeated stimuli nociceptors develop sensitization, expressed as an increase in response to magnitude and a decrease in response to threshold [21, 31, 32]. In this sense sensitization represents an increase in nociceptor excitability, mainly resulting from modifications of the chemical environment due to release of several inflammatory mediators (e.g., histamine, prostaglandins, serotonin, protons,

NGF, and substance P) [30]. These mediators act differently on nociceptors: some has a direct action, others reduce thresholds, and others have an indirect action [32]. Moreover, the inflammatory process may activate a subgroup of normally non-nociceptive fibers, known as "silent nociceptors": the result is an increase of pain signaling to the spinal cord. This contributes to visceral hyperalgesia [33].

A number of ion channels, neurotransmitter receptors, and trophic factors have been implicated in the development of peripheral sensitization [34]. Voltage-gated sodium channels play a crucial role in sensitization of visceral nociceptors, because they modulate action potentials propagation and control membrane excitability [12]. Tetrodotoxin-resistant currents are significantly present in nociceptive afferents [35] and have been found in dorsal root ganglion (DRG) neurons [36, 37]. In experimental models TTX-resistant currents show a relevant role in visceral nociceptor sensitization [38–41] and, in future, may be a target for developing new therapies [12].

2.3.2.1 Transient Receptor Potential Vallinoid

TRPV1 is a nonselective cation channel ubiquitously expressed on small to medium sized neurons [42], gated by noxious heat, low pH, and endogenous lipids [43], that serves a diverse range of sensory functions such as temperature sensing and hearing [44, 45]. It is preferentially expressed in visceral afferents compared to somatic in the lower lumbar cord of rats ([46].

The TRPV1 receptor may be activated by capsaicin and heat and is postulated to play an important role in mechano-transduction within the gastrointestinal tract [44, 47]. The relevance of TRPV1 in visceral innervation has been demonstrated by the painful effects of capsaicin application to viscera in several clinical and experimental studies [48–52]. In normal conditions, both viscera and spinal cord are not exposed to capsaicin or heat: the presence of TRPV1 in axons of visceral efferents rends the visceral efferents sensitive to mediators of inflammation. This means that they serve as nociceptors [13, 46, 53]. Upon activation, the TRPV1 receptor evokes a sensation of burning and pain and when associated with concomitant release of substance P, neurogenic inflammation occurs. As hydrogen ions strongly potentiate this activation it is not surprising that this ion channel has been widely studied in gastro-esophageal reflux disease, a disorder where excess acid exposure in the distal esophagus is central to the pathogenesis [54, 55]. There is accumulating evidence in humans linking increased TRPV1 expression with visceral hypersensitivity [56]. Interestingly, TRPV1 receptor antagonists have been found to ameliorate visceral hypersensitivity in a rat model [57]. These observations have led to considerable interest in the development of TRPV1 antagonists [58]. For instance, Krarup et al. [59] reported a randomized, placebo-controlled, double-blinded, crossover study investigating the effect of a TRPV1 antagonist (AZD1386) on experimentally induced esophageal pain. While pain thresholds to modalities such as mechanical and chemical stimulation were unaffected, AZD1386 did increase pain thresholds to heat stimuli within the esophagus. In a recent study, the effects of AZD1386 were investigated in patients with acute pain following a dental extraction [60]. Compared

to placebo, perceptible pain relief was significantly faster following AZD1386 although these differences were not appreciable when compared to naproxen.

2.3.3 The Role of Dorsal Columns

For many years the dorsal column-medial lemniscus system (DC) has been considered as a pathway not involved in pain perception. However experimental and clinical studies have demonstrated that the dorsal columns play an important role in mediating pain from viscera to the CNS [61, 62]. In fact, a limited midline myelotomy at dorsal level has been proven to significantly release pain in visceral cancer patients [63–67]. These clinical data were corroborated by experimental studies that showed that the activation of thalamic neurons was reduced by DC lesion not only following innocuous mechanical stimuli but also by visceral stimuli [68–71]. Actually it is thought that DC contains a contingent of ascending fiber with an important role in the perception of pain, especially in conditions of peripheral inflammation [62].

2.3.4 Central Processing

From the spinal cord, pain is transmitted to the brain through a number of pathways. The majority of afferents travel in the spinothalamic tract to the thalamus [29]. Thalamus projects to the insula, hypothalamus, amygdala, as well as to higher cortical levels (cingulate and prefrontal cortices) [29, 72–74]. The insula plays an important role for integrating visceral sensory and motor activity with limbic system inputs. This is an important factor in pain perception from the gut [75, 76]. The anterior cingulate and prefrontal cortices are parts of the medial pain system, which mediate affective, emotional, and cognitive components of pain experience [72, 74, 77]. Neuroimaging provided relevant data about human supraspinal processing of pain [78]. Several cortical areas are activated by painful stimuli, including the suprasylvian opercular area, the mid- and posterior insula, and the mid-anterior cingulate cortex [78]. The contribution of other regions, from the primary sensory cortex to anterior insula, to prefrontal and posterior parietal cortices, amygdala, and hippocampus is still debated [79–81]. The described areas would form a network for the processing of visceral pain stimuli, similar to that identified for somatic pain and defined “pain matrix” [78, 82].

It is thought that some afferents, which ascend in the spinal-reticular and not in the spinothalamic section, mediate the arousal and autonomic responses to pain, interacting with the reticular substance [72].

Finally, a population of afferents ascends in the spino-mesencephalic tract, which relates to a complex neuronal network including the periaqueductal gray, rostroventral medulla, and the dorsolateral pontine tegmentum. This network comprises the structural basis of descending pain control and modulates pain processing at the spinal level through descending inhibitory or facilitatory inputs [72].

2.3.5 Central Sensitization

Central sensitization differs substantially from peripheral sensitization [83]. As mentioned, peripheral sensitization is characterized by a reduction in threshold and an amplification of signal of nociceptors exposed to inflammatory mediators and damaged tissue [33, 83–87]. In fact, beyond the increased responsiveness (i.e., an increased synaptic efficacy) shown by central pain transmitting neurons [21, 88], in central sensitization novel inputs to nociceptive pathways are driven, including those that do not normally drive them, such as large low-threshold mechanoreceptor myelinated fibers to produce Aβ fiber-mediated pain [33]. The clinical correlate consists of increase in pain perception for a given painful stimulus (hyperalgesia). In addition to increasing the intensity and duration of pain at the stimulation site (primary hyperalgesia), repeated stimulation causes an enhancement of pain sensitivity in other non-affected areas or somatic sites (secondary hyperalgesia). This is consistent with the presence of extensive viscero-visceral and viscero-somatic convergence in dorsal horn neurons [78]. In this context repetitive visceral stimulation not only increases the intensity and duration of pain experienced from the site of stimulation (primary hyperalgesia) but also enhances pain sensitivity in somatic sites of referral and other non-affected areas (secondary hyperalgesia). As an example, repetitive colonic distension in human volunteers increased the perception of pain in the colon and also the abdominal area over which referred pain was perceived [89, 90]. In another human study [91], hydrochloric acid was infused into the distal esophagus. Pain thresholds were reduced not only in the acid-exposed region but also in the unexposed proximal region, suggesting the development of secondary hyperalgesia and central sensitization.

2.3.6 Descending Control of Visceral Pain

Several structures for the production of endogenous analgesia have been described in the brainstem, including the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) as far as pontine and medullary noradrenergic nuclei, including the locus coeruleus [78]. This data can help to explain how emotional states or attention level can have profound modulatory effects on pain perception [92]. Direct projections from the spinal dorsal horn and several supraspinal structures reach the periaqueductal gray and rostral ventromedial medulla. PAG projects to RVM which projects to superficial and deep laminae in the dorsal horn via the dorsolateral funiculus [92–94]. PAG stimulation can induce analgesia by activating indirect descending inhibitory projections to the spinal cord, including viscero-somatic neurons [95, 96]. RVM neurons have been functionally characterized and divided into ON and OFF cells. ON cells increase their firing just prior to the initiation of the nociceptive reflex, while OFF cells reduce firing [97, 98]. OFF cell activation is sufficient for analgesia, while the ON cells have a pronociceptive role in the context of pain [78].

The direct electrical stimulation of RVM can reduce or enhance visceromotor responses evoked by bladder or colorectal distension [99, 100] providing further evidence on the opposing roles of ON and OFF cells in visceral pain processing. In addition, colonic administration of capsaicin enhances function in ON-like cells and

reduces responses in OFF-like cells, thereby facilitating visceral pain [101]. Moreover the PAG-RVM complex contributes to the regulation of physiological parameters (heart rate, body temperature) and coordinated behaviors (aggression, defense, or maternal behavior,) supporting their role in discriminatory and affective components of pain processing [92].

2.3.7 The Role of Gut Microbiota in Visceral Pain

Man has a great variety of microorganisms that colonize different tissues that make up the body and perform different and important metabolic functions. Intestinal microbiota refers to the set of actual microorganisms of our intestine, while intestinal microbiome is the genetic heritage of the intestinal microbiota. The gut microbiome is thought to comprise over 1000 species and 7000 strains: although the bacteria constitute the major component, it includes viruses, protozoa, archaea, and fungi [102, 103]. Preclinical studies have demonstrated the role of the commensal microbiota for the development of an adequate pain sensitivity [103, 104]. Moreover, it has been demonstrated that in rats exposure to antibiotics during early life can increase visceral sensitivity, suggesting that alterations of the microbiota induced in specific period of life are crucial to the development of a sensitivity to pain [105]. Clinical studies have documented intestinal dysbiosis in patients affected by visceral pain, including inflammatory bowel disease, making the microbiota itself a possible target for treatment [106–108].

In inflammatory bowel disease patients, a shift in the diversity of bacteria species present in the bowel away from probiotic lactobacilli and bifidobacteria strains toward more pathogenic gram-negative species have been demonstrated [109–112]. The efficacy of probiotics in reducing symptoms (in terms of abdominal pain/discomfort or improved abdominal bloating/gassiness) in patients with inflammatory bowel disease has been demonstrated in some randomized control trials vs. placebo [113–117]. Finally, clinical data demonstrated a reduction of symptoms of abdominal pain (in patients with irritable bowel disease) induced by fecal microbiota transplantation [111, 118–120]. Although probiotics seem to have beneficial effects on improving irritable bowel disease symptoms, the mechanism of action is largely unknown [78, 103, 119]. Previous studies suggested a “peripherical” action, modulating gut inflammation by producing antimicrobial peptides that help to eliminate pathogenic bacteria, and improving the mucosal barrier function [119]. Another hypothesis is that the analgesic effects of probiotics should be due to the modulation of pro-analgesic endogenous opioid or endocannabinoid signaling [78, 121].

2.4 Conclusion

Despite being generally interpreted and consequently treated as somatic pain, visceral pain has its own peculiarities. In particular, there are many differences between somatic and visceral pain, from functional characteristics of the peripheral receptors

that innervate different visceral structure, to the lack of a separate visceral sensory pathway in the spinal cord and brain, to the very low proportion of visceral afferent fibers compared to those of somatic origin. The dorsal column-medial lemniscus system, once considered not involved in the mechanisms of pain transmission, is now recognized as an important structure in visceral nociception. Moreover, there are accumulating evidence on the importance of gut microbiota in the regulation of visceral pain, although the type of interaction between microbiota and brain is still far from being completely understood.

Future studies will allow greater knowledge of similarities and differences between visceral and somatic pain, thus enabling better patient management and more targeted therapies.

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Neuroinflammation and Chronic Pelvic Pain Syndrome

3

Rosalia Crupi, Marika Cordaro, and Salvatore Cuzzocrea

3.1 Chronic Pelvic Pain

Chronic pelvic pain (CPP) is well defined by the European Association of Urology (EAU) as "chronic or persistent pain perceived in structures associated to the pelvis in both men and women. It is frequently correlated with negative behavioral, cognitive, emotional, and sexual effects as well as with suggestive signs of lower urinary tract, bowel, pelvic floor, or gynecological dysfunction. For documented nociceptive pain that becomes chronic/persistent over time, pain must have been permanent or recurrent for at least 6 months. If the sensitization mechanisms of pain are well documented, the pain may be considered chronic, regardless of the time period" [1, 2]. CPP in the female or male genital zone may be localized to the vulva, vagina, or perineum, or may involve intra-abdominal organs, including uterus, ovaries, and fallopian tubes (females), or can involve the prostate, epididymis, scrotum, penis, or testicles (males) [3] (see Table 3.1).

These conditions lead to a substantial burden on limited health care resources. For example, an estimated £158 million are spent every year for the treatment of this disorder in the UK National Health Service [4, 5].

Additionally, in Europe, a study undertaken in 2004 by Breivik and colleagues [6] found that chronic pain of moderate maximum severe intensity occurs in 19% of adult Europeans, extremely disturbing the quality of their lives. There are some changes between states but not much spread is seen.

Considering the complexity of CPP, it is very difficult to treat and these lead to frustration for both patients and their physicians. Treatment should include

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Table 3.1 Classification and actual treatment of CPP in men and women

Urological aspect	Prostate pain syndrome	α-Blockers [152–159] Antibiotic therapy [160–163] Anti-inflammatory drugs [164–167] Opioids [168] 5-α-reductase inhibitors [169–171] Allopurinol [172–174] Phytotherapy [175–177] Pentosan polysulfate [178] Muscle relaxants [155] Pregabalin [179, 180] Botulinum toxin A [181, 182] Physical treatments [183–189] Surgical management [190, 191] Psychological treatment [192, 193]
	Bladder pain syndrome	Analgesics [168] Corticosteroids [194–196] Antiallergics [197–199] Antibiotics [200] Immunosuppressants [201–204] Gabapentin [205, 206] Pregabalin [207] Suplatast tosilate [208] Quercetin [209, 210] Tanezumab [211]
	Genital pain syndrome	Conservative treatment [183, 212–215] Surgery [216] Microsurgical denervation [216–218] Epididymectomy [219–224] Orchiectomy [1, 225] Vasovasostomy [226, 227]
	Urethral pain syndrome	Laser therapy [228] Behavioral therapy [229, 230]
Gynecological aspects	Dysmenorrhea	NSAIDs [231, 232]
	Infection	Treatment of infection depends on the causative organisms such as chlamydia or gonorrhea, or herpes simplex or urinary retention [232–234]
	Endometriosis and Adenomyosis	NSAIDs [231, 232] Laparoscopy [235–237]
	Organ prolapse	Mesh-excisional surgery [238, 239]
	Vaginal and vulvar pain syndromes	Psychological treatment [240–242]
Gastrointestinal aspects	Hemorrhoids	Excisional hemorrhoidectomy [243, 244] Rubber band ligation [243, 244] Hemorrhoidopexy [245]
	Anal fissure	Nitrates and calcium channel blockers [246] Botulinum toxin A injection [247] Sphincterotomy [248]

(continued)

Table 3.1 (continued)

	Proctitis	Antidepressants [249]
	Irritable bowel disease	Fecal microbiota transplantation [250] Dietary modifications [251] Exercise [252–254] Prebiotics and Probiotics [255] Antispasmodic drugs [256, 257] Peppermint oil [256, 258] Antidepressants [259–261] Drugs acting on opioid receptors [262, 263]
Peripherical aspect	Pudendal neuralgia	Conservative management [264, 265] Pudendal nerve block [266, 267] Pudendal nerve decompression [268–270]

multifactorial approaches involving counseling, psychosocial support, medication management, physical therapy, and interventional procedures [1].

3.2 Neuroinflammation

Neuroinflammation is described as an inflammatory reaction inside the spinal cord or brain [7]. Inflammatory events in the peripheral nervous system (PNS) or in the central nervous system (CNS) happen at diverse levels from those of other tissues and involved different types of cells [8, 9]. In particular, the primary distinction relies in the lack of resident dendritic cells in the CNS parenchyma and perivascular macrophages and vascular pericytes take over the functions of mature dendritic cells in the CNS [10]. Secondary, the stimulation of the innate immune cells of CNS parenchyma, such as astrocytes, microglia, and, in some regions, mast cells, may be amplified in clinical conditions such as trauma, stroke, neurodegenerative disease, or growth of a tumor [11–13]. Furthermore, the extravasation of immune cells and molecules towards the inflamed region, indispensable to stimulate complement cascades and maintain the immunity reaction, is crucial for the inflammatory response of the total organism.

However, in the CNS, the blood–CNS barrier limited the permeability of microvessels, making thus the entire inflammatory response incredibly different and difficult. Just stimulated T cells may infiltrate the barrier, but they do not elicit an effective response to inflammation equivalent with that observed in peripheral tissues, where dendritic cells are responsible for the adaptive immune reaction [14]. Due to these features, it is curious to point out that CNS replies to inflammatory events when these exert a direct effect on CNS, for example, in the case of pathogens and tissue injury, and when the inflammatory events are so austere that penetrating T cells are involved. With these clarifications it is crucial to understand the "neuroinflammation" terms that differentiates inflammatory response in the CNS from inflammation reaction in different tissues.

In this view the neuroinflammation terms are a reply of the CNS to altered homeostasis. Principally, one maybe two cell systems are competent to intermediate

this response: glia of the CNS, lymphocytes, macrophages of the hematopoietic system, and monocytes [15]. The actions encouraged by the neuroinflammations are classified as:

- Homeostatic: when it involves different events such as vasodilation or the release of cytokines and neurotrophic factors
- Maladaptive or neurotoxic: when it is characterized by the release of pro-inflammatory factors or the breakdown of blood–CNS barrier
- Anti-inflammatory: when, contrary to what was said above, it involves the release of pro-inflammatory cytokines, neurotrophic factors, neurotransmitters, and cell adhesion molecules

After injury neuroinflammation is dynamically coordinated by a complex network of regulatory mechanisms, which confine the hypothetically damaging effects of persistent inflammation.

In particular, chronic, uncontrolled inflammation is characterized by overexpression of reactive oxygen species (ROS), cytokines, such as TNF-α and IL-1β, and other inflammatory mediators, such as inducible nitric oxide synthase (iNOS).

All these inflammatory molecules are detected following trauma to the CNS, and are involved by employment and trafficking of neutrophils and peripheral macrophages to the injury place. Anyhow, when the inflammatory event is protracted, and the hyperactivation of macrophages is continued, it overpowers the bounds of physiological control and leads to a series of deleterious effects that involve the activation of pro-inflammatory signaling pathways, increase oxidative stress, and death of nearby neurons that provide to the pathogenesis of chronic pain, such as neuropathic pain or neurodegeneration [16, 17].

Last but not least is the role played by neuroinflammation in animal pain models of neuropathic, incisional, inflammatory, and central pain and it is also closely associated with a number of comorbidities of chronic pain such as diabetes, sleep and anxiety disorders, obesity, and depression [18] and for these reasons targeting excessive neuroinflammation can offer new therapeutic approaches for the management of chronic pain and related neurological and psychiatric disorders.

3.3 Microglia and Astrocytes in Chronic Pain

The involvement of microglia and astrocytes in pain processing has been progressively recognized by many laboratories using varied procedures and animal models of temporary or persistent pain. These activations play a crucial role during neuronal recovery after central or peripheral injury [19]. Microglia are macrophage-like cells in the CNS that originate from bone marrow-derived monocytes and that migrate during perinatal development. They are heterogeneously disseminated throughout the CNS. Under physiological situations, microglia are not inactive as many researchers initially assumed, but it has been shown that microglia dynamically sense their environment with their ramified processes [20–22]. In particular, microglia energetically cooperate with synapses to regulate their organizations and

functions in healthy brain [23]. During growth, microglial processes can engulf synapses, and synaptic pruning by microglia, which includes the activation of the complement system, is necessary for normal brain development [24, 25].

During activation, microglia exhibit morphological changes, such as a changing into the amoeboid form, from ramified, to and upregulation of microglial markers such as CCR3/CD11b, major histocompatibility complex II [MHC II], or ionized calcium-binding adaptor molecule-1 [IBA1] [20, 26–28].

Various studies have shown that microglia plays a critical role in neuropathic pain development as well as acute inflammatory pain [29–33]. For instance, it has been shown that minocycline, a nonselective microglia inhibitor, reduces inflammatory or postoperative or neuropathic pain. However, its function in decreasing neuropathic pain in the late phase is restricted [32, 34–36].

Astrocytes are the most abundant cells in the CNS and play several active functions in acute and chronic neurological diseases such as stroke or ischemia [37]. In contrast to microglia and oligodendrocytes, astrocytes formed physically coupled networks intermediated by gap junctions, which, among other roles, simplify intercellular transmission of Ca^{2+} signaling, exchange of cytosolic contents, and display oscillations in ion permeability across astrocytic networks. Gap junction communication is mediated by homo- and heteromeric associations of hemichannels, such as connexin-43 (Cx43), the most prevalent connexin expressed in astrocytes [38]. Although astrocytes are naturally immune labeled by glial fibrillary acidic protein (GFAP).

It is important to note that, every astrocyte forms a nonoverlapping territory or domain, which all together resemble a lattice framework, looking crystalline in nature. On the other hand, the implications of this organization are not fully understood; it becomes lost when astrocytes transition to reactive states [37, 39, 40]. Moreover, astrocytes have wide-ranging interactions with both cerebral blood vessels and synapses, and through these connections they control the increase in blood flow induced by synaptic activity. The astrocyte-mediated blood flow increased is fundamental to the blood-oxygen-level-dependent (BOLD) signal detected by functional magnetic resonance imaging (fMRI) [39]. It is assessed that, in rodents, a single astrocyte can enwrap 140,000 synapses and 4–6 neuronal somata, and can interact to 300–600 neuronal dendrites [40–42]. During synaptic transmission, close contact with neurons and synapses allows astrocytes not only to help and nourish neurons but also to control the external chemical environment. The increasing appreciation for active roles of astrocytes has led to the proposal of a "tripartite synapse" theory, founded on the facts that glia respond to neuronal activity with an increase of their internal Ca^{2+} concentration and cause the release of chemical transmitters from glia themselves, and glial transmitters through a feedback regulation of neuronal activity and synaptic strength [43, 44]. According to this, astrocytic processes are active components of synapses, in addition to pre- and postsynaptic components [45]. On the other hand, active contribution to synaptic activity remains just a possibility because several recent studies have challenged this theory, by demonstrating that alterations in astrocytic Ca^{2+} do not modulate synaptic transmission [46–48].

Due to important modifications in the expression of membrane proteins as well as neural circuits during growth, it is feasible that the notion of receptor-mediated Ca^{2+} signaling will be extended to include other intracellular signaling pathways as a main element defining astrocytic involvement in greater neural function. For example, in the young or adult rodent brain, glutamate-dependent neuroglial Ca^{2+} signaling is different [49–51]. Freshly, it has been demonstrated that receptor-mediated increases in astrocytic Ca^{2+} can control neural network activity by active uptake of extracellular K^+ [52]. Considering that the extracellular concentration of K^+ is an important determinant of the resting membrane potential and thereby of neuronal activity, active uptake of K^+ represents a simple yet powerful tool for rapid variation of neural networks.

Studies using astroglial toxins or astroglial aconitase inhibitor or inhibitors of the astroglial enzyme glutamine synthetase in adult animals suggest that astrocytes play a key role both for the stimulation and preservation of inflammatory and for neuropathic pain [41, 53–60].

Models of neuropathic pain such as rhizotomy and spinal nerve ligation have shown proliferation of spinal cord astrocytes [61, 62]. Conversely, inhibiting astrocyte proliferation in the spinal cord was shown to reduce neuropathic pain [61].

3.4 Molecular Mediators in Chronic Pain

A main problem with regard to glial pain control is understanding how glial mediators are generated and released. In particular, glia produce large molecules such as chemokines, cytokines, proteases, and growth factors, as well as small molecules like glutamate, prostaglandin E2 (PGE2), ATP, and D-serine. These glial mediators can control neuronal and synaptic activity and, most important, pain sensitivity. Among the most well-studied glial mediators are pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-1β.

These cytokines are upregulated in spinal cord glia after nerve injury, inflammation, and others, and they are involved in the development and maintenance of inflammatory, neuropathic, and cancer pain and morphine tolerance [63–66].

In relation to its well-documented role in modulating peripheral sensitization, TNF-α plays a main role in generating central sensitization and persistent pain [67–73]. IL-1β is induced in astrocytes and microglia after bone cancer, inflammation, and nerve injury [55, 67, 74–78]. It was clearly demonstrated that the inhibition of spinal and brain IL-1β signaling reduces inflammatory, neuropathic, and cancer pain and enhances morphine analgesia [55, 66, 74, 76, 79–81]. Also, chemokines are produced by glial cells, particularly in astrocytes and in neurons [82, 83]. In primary cultures of astrocytes, TNF-α induced rapid expression of (C-C motif) Ligand 2 (CCL2), C-X-C motif chemokine 10 (CXCL10), and C-X-C motif chemokine 1(CXCL1) [84]. Spinal injection of TNF-α-activated astrocytes leads to constant mechanical allodynia through CCL2 release [85]. Additionally, CCL2 expression is further increased in astrocytes of the medullary dorsal horn and contributes to trigeminal neuropathic pain and in spinal nerve ligation induces CCL2

release in spinal astrocytes, and it was observed that intrathecal administration of an MCP-1 neutralizing antibody diminished neuropathic pain [84, 86]. In fact, mice with CCL2 overexpression in astrocytes display pain hypersensitivity [87].

Moreover, growth factors are well known to be induced in spinal glia by nerve injury. In particular, brain-derived neurotrophic factor (BDNF) was upregulated during nerve ligation in spinal microglia, via activation of P2X4 and p38 [88, 89]. Additionally, spinal injection of ATP-activated microglia is sufficient to stimulate mechanical allodynia via releasing BDNF, and, equally, neuropathic pain is repressed by spinal blockade of the BDNF receptor TrkB [30]. Furthermore, treatment of microglial cultures with morphine increases BDNF release, which does not require l-opioid receptor and TLR [90]. BDNF is also induced in dorsal root ganglion (DRG) neurons after nerve injury and can be produced from primary afferents in the spinal cord [91, 92]. Unlike BDNF, basic fibroblast growth factor (bFGF or FGF-2) is produced in activate astrocytes of the spinal cord in the late phase (3 weeks) of nerve injury [56].

Intrathecal infusion of bFGF produces persistent activation of spinal astrocytes through the upregulation of P-JNK and GFAP and sustained mechanical allodynia and chronic pain [56]. On the other hand, intrathecal administration of a bFGF-neutralizing antibody reduces established neuropathic pain [93].

After nerve injury, also proteases are upregulated in spinal glia. It is well known that, spinal nerve ligation induces matrix metalloprotease-2 (MMP-2) in spinal cord astrocytes and DRG and satellite glial cells (SGCs) in the late phase of neuropathic pain to maintain neuropathic state, via activation of IL-1β and ERK [94].

Nerve injury additionally stimulates the production of cathepsin S in spinal microglia [95] and tissue-type plasminogen activator (tPA) in spinal astrocytes to enhance neuropathic pain [96]. A recent study indicated that nerve injury also increased the production of thrombospondin-4 (TSP4), an extracellular matrix glycoprotein, in spinal cord astrocytes correlated for the development of neuropathic pain and for synaptogenesis [97, 98].

To increase and to maintain the pain state, astrocytes produce small molecule mediators such as D-serine, ATP, and glutamate [41].

On the other hand, the anti-inflammatory and antinociceptive mediators IL-4, IL-10, and TGF-β were produced by glial cells for the recovery and resolution of pain [20, 99–102]. Improvement of endogenous production of IL-10 via gene therapy has been demonstrated to produce long-term relief in neuropathic pain. Of interest, a possible off-target effect of high doses of siRNAs is to induce IFN-α in spinal astrocytes for eliciting antinociceptive effects [103, 104].

3.5 Targeting Excessive Inflammation as a Therapy for Neuropathic Pain

There is currently strong suggestion from preclinical studies, and more restricted evidence in clinical studies, that damage to the nervous system can lead to a maladaptive inflammatory reaction contributing to the generation of persistent pain.

There remain various obstacles to making an interpretation of this information into patient benefit. For this reason, there are several challenges in the design of appropriate clinical trials.

Using pain animal models are most successful at the time of injury, while delayed treatment is a more likely clinical scenario. On the other hand, only a subset of patients develop neuropathic pain after a lesion and we do not yet have effective predictive models. Increasingly evidences suggest that there are multiple pathophysiological mechanisms leading to persistent pain after nerve injury. It would be of great benefit to use either clinical or molecular biomarkers to individualize treatment, for example, targeting excessive inflammation only in those patients where there is evidence of an ongoing inflammatory response [105]. Some agents that modulate inflammation are already being used in selected groups of patients with neuropathic pain, although there is often a lack of evidence from the trial. It is well known that corticosteroids suppress pro-inflammatory cytokine expression and cell-mediated immunity. They are administered by several routes for the treatment of several neuropathic pain conditions, such as post-herpetic neuralgia or radicular back pain; however, definitive evidence for their efficacy is absent because of the scarcity of placebo-controlled studies and, in some cases, trials have shown side effects [106–109].

Another approach, recently studied, involved the use of select cytokines inhibitors [110, 111]. One probable trouble is the significant redundancy in the action of cytokines. Furthermore, as with corticosteroid suppression of the immune system, if these agents are given systemically they may be associated with an appreciably amplified risk of infection. The use of pro-resolution agents such as resolvins would be one strategy that could use a wide anti-inflammatory intervention [112].

The inhibition of microglial function is another novel option. Minocycline clinical trials for the prevention of postoperative intercostal pain, an optimal situation for testing this agent, are ongoing (NCT0131 4482).

Propentofylline decreases the production of free radicals and microglia activation. A randomized controlled trial of this agent did not find efficacy in the treatment of post-herpetic neuralgia [62]. Further approaches would be to target key ligand-gated ion channels expressed in microglia such as P2X4 and P2X7 or downstream signaling pathways that drive microglia towards an effector state such as p38 MAP kinase.

In a small double-blind crossover trial, the p38 mitogen-activated protein kinase inhibitor SB-681323 significantly decreased the daily pain score in patients with neuropathic pain [8, 113].

3.6 Clinical Significance and Future Perspectives

The delivery of anti-inflammatory drugs to the CNS is critical, given the significant role of key neuroinflammation in keeping chronic pain. Neuroinflammation consequential from neuroglial and neuro-immune interactions not only assists as a driving force for chronic pain but is also involved in other neurological and

psychiatric diseases such as Alzheimer's and Parkinson's disease, multiple sclerosis (SM), autism, and others, as well as in cognitive deficits after major surgeries [114, 115]. Chronic pain is, in fact, commonly linked with depression, anxiety, sleep disorders, and cognitive decline, which are clinical sequelae of particular concern to the growing aging population which has increasingly high prevalence of chronic pain. Neuroinflammation and astrocyte reactivity is also connected with chronic pain in postmortem human spinal cord samples [116]. The development of effective new treatments for the prevention and resolution of neuroinflammation and postoperative pain is mandatory. Actually to counteract neuroinflammatory processes a new therapeutic approach is represented by the use of natural compound. In this chapter we focused our attention on some recent evidences that involved the use of aliamides, alone, or in association with antioxidant molecules.

3.7 PEA

N-Acylethanolamines are classified as naturally occurring lipidic mediator molecules composed of a fatty acid and ethanolamine, collectively namely "fatty acid ethanolamines" (FAEs). They are endogenous molecules involved in endogenous protective mechanisms, activated in the body as a result of different types of tissue damage or stimulation of inflammatory responses and nociceptive fibers. The members of FAE family are the endocannabinoid N-arachidonoylethanolamine (anandamide, or 5Z,8Z,11Z,14Z)-N-(2-hydroxyethyl)icosa-5,8,11,14-tetraenamide) and its congeners N-stearoylethanolamine (N-(2-hydroxyethyl)-stearamide), N-oleoylethanolamine (N-2-hydroxyethyl- 9(Z)-octadecenamide), and N-palmitoylethanolamine (PEA, or palmitoylethanolamide) (N-(2-hydroxyethyl)- hexadecanamide).

PEA and its congeners are formed from N-acylated phosphatidylethanolamine (NAPE) by several enzymatic pathways [117], the principal one involving a membrane-associated NAPE-phospholipase D which generates the respective NAE and phosphatidic acid. This enzyme is able to convert N-palmitoyl-phosphatidyl-ethanolamine into PEA. In the mammalian brain, NAEs are hydrolyzed by: (1) fatty acid amide hydrolase in the endoplasmic reticulum, which breaks down NAEs into the corresponding fatty acid and ethanolamine; (2) lysosomal NAE-hydrolyzing acid amidase (NAAA) [118]. NAAA is found mainly in macrophages, where it hydrolyzes NAEs with less than 18 carbon atoms, i.e., PEA, but not N-oleoylethanolamine and N-stearoylethanolamine. In contrast, fatty acid amide hydrolase hydrolyzes all three NAEs. PEA is abundant in mammals; there are evidences for the presence of PEA as well as other FAEs in marine species and sea urchin ovaries [119]. Biologically, PEA is produced and hydrolyzed by microglia [120], inhibits mast cell activation [121], and increases in glutamate-treated neocortical neurons ex vivo and in cortex after CNS injury, as well as in muscle dialysate from women with chronic neck/shoulder pain [122].

PEA levels are also increased in a mouse model of experimental allergic encephalomyelitis [123].

Mechanistically PEA may be a ligand for peroxisome proliferator activated receptor α (PPARα), one of a group of nuclear receptor proteins that function as transcription factors regulating the expression of genes. In particular, the α- and γ-isoforms of PPAR are associated with pro-inflammatory effects. Moreover, in PPARα null mice or blocked by PPARα antagonists the anti-inflammatory, antinociceptive/anti-neuropathic, and neuroprotective effect of PEA were not detected [124]. PEA is produced through an *"on-demand"* synthesis within the lipid bilayer where N -phosphatidylethanolamine-specific phospholipase D (NAPE-PLD) releases it from its membrane precursor, N-palmitoyl phosphatidylethanolamine.

An *"entourage effect"* has also been hypothesized to clarify the pharmacological actions of PEA, whereby PEA enhances the anti-inflammatory and antinociceptive activity of other endogenous compounds by potentiating their affinity for a receptor or by inhibiting their metabolic degradation.

Anandamide and its congeners like PEA have in common the transient receptor potential vanilloid type 1 (TRPV1) receptor that is activated by noxious heat, low pH, and capsaicin. Anandamide itself is a TRPV1 receptor agonist, and PEA enhances anandamide stimulation of the human TRPV1 receptor in a cannabinoid CB2 receptor antagonist-sensitive fashion—which could be interpreted as PEA acting indirectly by potentiating anandamide actions. Mast cells and microglia reportedly express TRPV1 receptors [125].

3.8 Polydatin

Polydatin (PO), also called piceid, is a traditional Chinese medicine, detected in many daily diets food that has wide-ranging pharmacological activities [126, 127]. There are four main derivatives of PO in nature, including trans-polydatin, trans-resveratrol, cis-polydatin, and cis-resveratrol [128].

PO has a range of biological effects, such as the ability to protect lung, brain, heart, and intestine against ischemia-reperfusion (I/R) injury, anti-platelet aggregation, as well as anti-inflammatory, anti-shock, and anti-oxidation effects [129–135]. Additionally, two studies done in the last year demonstrated that PO protects against acetaminophen-induced hepatotoxicity in mice and suppresses nucleus pulposus cell senescence, promoting matrix homeostasis and attenuating intervertebral disc degeneration in rats [136, 137].

3.9 PEA and Polydatin as Future Treatment of Chronic Pelvic Pain

Preclinical studies about the management of chronic pain with the association of PEA and PO showed a significant reduction in the inflammatory process and pain associated with an experimental rat model of surgically induced endometriosis or carrageenan-induced acute inflammation as well as possess the ability to decrease

prostate weight, DHT production, inflammation and oxidative stress process and apoptosis dysregulation in an experimental model of testosterone induced benign prostatic hyperplasia [138–140].

Clinical trials in which PEA/PO was first used was published in 2010 [141, 142], suggesting that a combination of micronized PEA/PO was efficient in endometriosis-related chronic pelvic pain. Indraccolo et al. [142] reported only 4 cases of endometriosis treatment with oral micronized PEA/PO (400 mg/40 mg) twice a day for 3 months, while Cobellis et al. [143] treated 18 patients in one arm of a randomized trial with micronized PEA/PO (200 mg/20 mg) orally, three times a day for 3 months. Both studies showed an improvement in mean pain visual analog scale (VAS) scores for chronic pelvic pain and other endometriotic pains (with improvement in the micronized PEA/PO arm versus placebo arm in the randomized trial [143]). The above observations were substantiated by results of VAS score improvement in a study on 610 patients [144] treated with micronized PEA (600 mg twice daily) for chronic pain due to several causes, leading us to speculate that micronized PEA is effective also on chronic pelvic pain, even in the presence of endometriosis.

Additionally, another study provides preliminary evidence on the efficacy and safety of um-PEA/PO as an add-on treatment to conventional pharmacological regimens in patients suffering from IC/BPS, showing a significantly decreased pain in 75% of patients [145].

In another set of experiment, Tartaglia and colleagues considered the effectiveness of an oral combination of PEA and trans-polydatin in the treatment of primary dysmenorrhea in healthy adolescents and young women and found a reduction in symptoms, exerting a neuroprotective and antinociceptive effect during primary dysmenorrhea [146].

Interestingly, all mechanistic studies showing a benefit of active treatment in the management of several pathologies failed to exactly clarify the exact mechanism of action of the active compound, confirming the complexity of these type of studies [147–149]. Whether the PEA/PO effect is centrally related, secondary to mast cell stabilization or to modulation of the endocannabinoid system remains to be further investigated [150, 151].

In fact, confirmation of these initial findings will require randomized, double-blind, placebo-controlled clinical trials of sufficient power to assess rates of respondents in subgroups of patients, in order to fully appreciate the efficacy of micronized PEA/PO combination as a therapy for endometriosis, together with cohort studies to assess long-term effects of such therapy [142].

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Part II

The Organs, Pelvic Functions and Pain

Chronic Pelvic Pain and Chronic Pelvic Pain Syndrome: Classification and Epidemiology

4

Maria Angela Cerruto

4.1 Introduction

It is a constant presence, noisy in silence, a worm that demands all attention absorbing all social energy. It is like a stubborn tormentor who torments you day and night. The only way to live would be to get rid of it, escape from captivity in which it relegates all those who suffer from it. Its name in Pain.

Pain may be defined as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*" [1]. Pain is always subjective and often is associated with actual or potential tissue damage. However, many people report pain in the absence of tissue damage or any likely pathophysiological cause. Thus, pain should be characterized by type, frequency, duration, precipitating and relieving factors and by location.

Pain is recognized as an important contributor to the global burden of disability. Although technically defined as an experience [2], pain is also a symptom and, in some cases, especially when persistent and without clear aetiology, it may be a pathologic entity of self-propagating central nervous system sensitization.

Because these sensitized central neural pathways regulate pain, sleep and mood, chronic pain in these cases can both predate and follow the development of depression, anxiety and insomnia. The term used to describe this phenomenon is controversial and evolving along with knowledge about its physiologic underpinnings garnered from functional brain imaging and neurophysiologic research [3]. "Central sensitization syndrome" (CSS) is the most general term and the one used here, although "centralized pain" also is used to describe an ongoing peripheral insult or inflammatory process resulting in sensitization of the central nervous system.

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Fibromyalgia, chronic widespread pain, and even so-called somatoform disorders are all diagnoses reflecting central nervous system sensitization causing diffuse chronic pain without clear aetiology. Widespread hyperalgesia and allodynia often are found in these patients, but objective sensory testing is limited to research settings, and validated diagnostic values for CSS are elusive [4]. Chronic prostatitis/pelvic pain, chronic abdominal pain and irritable bowel syndrome often coexist in a patient with CSS. Actually, pain, discomfort and pressure may be part of a spectrum of abnormal sensation felt by the individual at genital, bowel and lower urinary tract level [5]. Pain produces the greatest impact on the patient and may be related to different lower urinary tract symptoms (LUTS) and can be felt before, during and/or after micturition, or to be continuous.

4.2 Definitions

When we talk about *pelvic pain* it is less well defined than, for example, bladder, urethral or perineal pain, and is less clearly related to the micturition cycle or to bowel function and is not localized to any single pelvic organ [5].

According to EAU definition [6], ***Chronic Pelvic Pain (CPP)*** is *"chronic or persistent pain perceived* in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction". [*Perceived indicates that the patient and clinician, to the best of their ability from the history, examination and investigations (where appropriate) has localised the pain as being discerned in a specified anatomical pelvic area.]*

Chronic pelvic pain syndrome (CPPS) is the occurrence of CPP when there is no proven infection or other obvious local pathology that may account for the pain. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. CPPS is a sub-division of CPP [6].

4.3 Classification

Much debate over the classification of CPP has occurred, is ongoing and will continue in the future. Classification involves three aspects of defining a condition: phenotyping, terminology and taxonomy [6].

Phenotyping refers to the description of all observable characteristics of any the condition, as the presence of Hunner's ulcers and glomerulation on cystoscopy that can be associated with chronic bladder pain, whereas other bladder pain conditions may have a normal appearance on cystoscopy. Irritable bowel syndrome (IBS) can present in two different phenotypes: with diarrhoea or that with constipation. Phenotyping may be based upon both known and unknown mechanisms.

Terminology is extremely complex and multiform: interstitial cystitis, painful bladder syndrome and bladder pain syndrome (BPS) were used to name the phenotype. Nowadays, the term *bladder pain syndrome* is preferred by several Societies. "Syndrome" indicates not only the crucial role of the nervous system in generating the sensations is thought to be pivotal, but also the multitude of consequences of the chronic pain: behavioural, emotional, cognitive, functional and sexual. Terms that end in *"itis"* in particular should be avoided unless infection and or inflammation is proven and considered to be the cause of the pain [7].

Taxonomy places the phenotypes into a relationship hierarchy. The EAU approach sub-divides CPP into conditions that are pain syndromes and those that are non-pain syndromes, as well-recognized pathologies (e.g., infection, neuropathy or inflammation) [6].

4.3.1 Classification of CPPS

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

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 one to compare disorders such as bladder and bowel pain syndromes, thus facilitating research and treatment.

The EAU has led the sub-divisions of the pain syndromes as follows [6]:

1. The pain syndromes are defined by a process of exclusion.
2. A sub-division phenotype should only be used if there is adequate evidence to support its use.
3. In 2004 the panel introduced the concept of managing the polysymptomatic nature of CPP, since then others have developed their own schemes, such as Nickel's UPOINT [8], modified by Magri et al. [9]. In light of these and other publications, the symptom classification table has been updated (Table 4.1).

The debate in relation to sub-dividing the pain syndromes remains ongoing. As more information is collected suggesting that the central nervous system (CNS) is involved, and indeed may be the main cause of many CPP conditions (e.g., bladder, genitalia, colorectal or myofascial), there is a general tendency to move away from end-organ nomenclature. 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. The classification has been set up according to the axis system used by IASP [1, 6].

The original EAU classification was inspired by the IASP classification [1, 6] and much work around what has become known as "pain as a disease" and its associated psychological, behavioural, sexual and functional correlates. After 10 years of work developing the initial ideas, an updated version was accepted by the IASP Council for publication in January 2012.

Table 4.1 EAU classification of chronic pelvic pain syndromes (Reproduced with permission)

Axis I Region		Axis II System	Axis III End organ as pain syndrome as identified from Hx, Ex and Ix	Axis IV Referral characteristics	Axis V Temporal characteristics	Axis VI Character	Axis VII Associated symptoms	Axis VIII Psychological symptoms
Chronic pelvic pain	Specific disease-associated pelvic pain	Urological	Prostate	Suprapubic Inguinal urethral Penile/clitoral Perineal rectal Back buttocks thighs	ONSET Acute chronic	Aching Burning stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance dysfunctional flow urgency incontinence	ANXIETY About pain or putative cause of pain
			Bladder					
	OR		Scrotal testicular Epididymal		ONGOING sporadic Cyclical continuous			Catastrophic thinking about pain
	Pelvic pain syndrome		Penile urethral				GYNAECOLOGICAL Menstrual menopause	DEPRESSION Attributed to pain or impact of pain
			Post-vasectomy		TIME filling Emptying immediate post late post			
		Gynaecological	Vulvar vestibular clitoral				GASTROINTESTINAL constipation Diarrhoea Bloatedness urgency Incontinence	Attributed to Other causes
			Endometriosis-associated		TRIGGER Provoked Spontaneous			Unattributed
			CPPS with cyclical exacerbations					
			Dysmenorrhoea					
		Gastrointestinal	Irritable bowel				NEUROLOGICAL Dysaesthesia hyperaesthesia Allodynia Hyperalgesia	PTSD SYMPTOMS Re-experiencing avoidance
			Chronic anal					
			Intermittent chronic anal					
		Peripheral nerves	Pudendal pain syndrome					
		Sexological	Dyspareunia				SEXUOLOGICAL satisfaction female dyspareunia Sexual avoidance erectile dysfunction medication	
			Pelvic pain with sexual dysfunction					
		Psychological	Any pelvic organ					
		Musculoskeletal	Pelvic floor muscle abdominal muscle spinal				MUSCLE function impairment Fasciculation	
			Coccyx				CUTANEOUS trophic changes sensory changes	

Hx History, *Ex* Examination, *Ix* Investigation, *PTSD* post-traumatic stress disorder

Pain perception in CPPS may be also 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 localized to a single organ, some specialists may wish to consider using an end-organ term such as bladder pain syndrome (Table 4.2). 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 localized to more than one organ site, the term CPPS should be used.

Many CPPSs are associated with a range of concurrent negative *psychological, behavioural and sexual consequences* that must be described and assessed. Examples that need to be considered are depression, anxiety, fears about pain or its implications, unhelpful coping strategies, and distress in relationships [6]. 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 [6]. It is suggested that CPPS sometimes creates a sense of helplessness that can be reported as overwhelming, and may be associated with the refractory nature of the patients' symptoms. It is important to note that many of these biopsychosocial consequences are common to other persistent pain problems but may show varying degrees of importance for any one individual suffering from CPPS [6]. In all patients with CPPS, these consequences must be clearly described as part of the phenotype (where the term phenotype is used to indicate the observable characteristics of the syndrome).

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 [6]. That is, they are disorders characterized 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 abnormal. The term is not used in the sense of a psychiatric functional disorder. Many CPPSs are associated with functional abnormalities at a local and even systemic level. These also need to be defined as a part of the phenotype. Functional pain disorders may not express significant pathology in the organs that appear responsible for the primary symptoms, but they are associated with substantial neurobiological, physiological and sometimes anatomical changes in the CNS [6].

4.4 Dyspareunia

Dyspareunia can be described as continuous unremitting or intermittent pain associated with intercourse. It can be classified based on the location of the pain—entry or deep dyspareunia, or based on when the pain was first experienced—primary or secondary dyspareunia. There are different causes of dyspareunia and some of the

Table 4.2 Chronic pelvic pain syndromes (modified from EAU guidelines 2019) (Reproduced with permission)

1. Urological pain syndromes	**Prostate pain syndrome** Prostate pain syndrome (PPS) is a persistent or recurrent episodic pain convincingly reproduced by prostate palpation, without infection or other local pathology. PPS is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. The terms "chronic prostatitis" and "prostadynia" are still used although inappropriate. Please note that some of the authors of the IASP document disagree with this term and suggest that CPPS of the male is used instead of PPS, which has been agreed by the majority
	Bladder pain syndrome Bladder pain syndrome (BPS) is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and daytime and/or night-time urinary frequency, without infection or other local pathology. BPS is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. BPS is believed to represent a heterogeneous spectrum of disorders. There may be specific types of inflammation as a feature in subsets of patients. Localization of the pain can be difficult by examination, and consequently, another localizing symptom is required. Cystoscopy with hydrodistention and biopsy may be indicated to define phenotypes. Old terms as "interstitial cystitis", "painful bladder syndrome", and "PBS/IC" or "BPS/IC" are no longer recommended
	Scrotal pain syndrome Scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localized within the organs of the scrotum, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction, without infection or other local pathology. Scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Scrotal pain syndrome is used when the site of the pain is not clearly testicular or epididymal, nor in the skin of the scrotum, but perceived within its contents
	Testicular pain syndrome Testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction, without infection or other local pathology. Testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences
	Epididymal pain syndrome Epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction, without infection or other local pathology. Epididymal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences
	Penile pain syndrome Penile pain syndrome is the occurrence of pain within the penis (but not primarily in the urethra), without infection or other local pathology. Penile pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction
	Urethral pain syndrome Urethral pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the urethra, without infection or other local pathology. Urethral pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Urethral pain syndrome may occur in men and women
	Post-vasectomy scrotal pain syndrome Post-vasectomy scrotal pain syndrome is a scrotal pain syndrome that follows vasectomy, 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 a special form of scrotal pain syndrome

Table 4.2 (continued)

2. Gynaecological pain syndromes: External genitalia	**Vulvar pain syndrome** Vulvar pain syndrome is the occurrence of persistent or recurrent episodic vulvar pain, without infection or other 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. 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 term "vulvodynia" used by the International Society for the Study of Vulvovaginal Disease (ISSVD) represents vulvar pain that is not accounted for by any physical findings, a "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)
	Generalized vulvar pain syndrome Generalized vulvar pain syndrome refers to a vulvar pain syndrome in which the pain/burning cannot be consistently and precisely localized 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
	Localized vulvar pain syndrome Localized vulvar pain syndrome refers to pain that can be consistently and precisely localized 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) and can be sub-divided into: • Vestibular pain syndrome • Clitoral pain syndrome
3. 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 pelvic pain syndrome with cyclical exacerbations Chronic pelvic pain syndrome with cyclical exacerbations covers the nongynaecological organ pain that frequently shows cyclical exacerbations (e.g., IBS or BPS) as well as pain similar to that associated with endometriosis/adenomyosis but where no pathology is identified. This condition is different from dysmenorrhoea, in which pain is only present with menstruation
	Dysmenorrhoea Dysmenorrhoea is pain with menstruation that is not associated with well-defined pathology. Dysmenorrhoea needs to be considered as a chronic pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual or emotional consequences

(continued)

Table 4.2 (continued)

4. 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. IBS 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 [12]: 3 months of continuous or recurring symptoms of abdominal pain or irritation that may be relieved with a bowel movement, may be coupled with a change in frequency, or may be related to a change in stool consistency. Two or more of the following are present at least 25% of the time: change in stool frequency (> 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 anal pain syndrome Chronic anal pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the anus, in the absence of proven infection or other obvious local pathology. Chronic anal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction
	Intermittent chronic anal pain syndrome Intermittent chronic anal pain syndrome refers to severe, brief, episodic pain that seems to arise in the rectum or anal canal and occurs at irregular intervals. This is unrelated to the need to or the process of defecation. It may be considered a sub-group of the chronic anal pain syndromes. It was previously known as "proctalgia fugax" but this term is no longer recommended
5. Musculoskeletal system	**Pelvic floor muscle pain syndrome** Pelvic floor muscle pain syndrome is the occurrence of persistent or recurrent episodic pelvic floor pain. There is no proven well-defined local pathology. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. This syndrome may be associated with 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
	Coccyx pain syndrome Coccyx pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the region of the coccyx, in the absence of proven infection or other obvious local pathology. Coccyx pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction

most important causes include the following: vulvodynia, postpartum dyspareunia, endometriosis, inadequate vaginal lubrication or arousal, and other anogenital causes such as haemorrhoids and anal fissures.

4.5 Perineal Pain Syndrome

It is the occurrence of persistent or recurrent episodic perineal pain, which is either related to the micturition cycle or associated with symptoms suggestive of urinary tract or sexual dysfunction [6]. There is no proven infection or other obvious pathology. It 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. Thus, in men, the pain is localized in the area between the testicles and the anus; in women, the area between the vagina and the anus. It should be differentiated from the

pudendal neuralgia which is a specific disease associated with pelvic pain that is caused by nerve damage [6].

4.6 Epidemiology

There are insufficient data available on the epidemiology of CPP and CPPS to design a complete and correct *incidence* of this disorder.

CPP *prevalence* is comparable with global prevalence of asthma (4.3–8.6%) [10] and 1-month prevalence of low back pain (23.2 ± 2.9%) [11]. The prevalence for women in reproductive ages is between 14 and 24% and about 14% of women experience CPP at least for one time during their life [12].

Overall, CPP *prevalence* in women ranged between 5.7% and 26.6% [13]. Actually, the worldwide prevalence variation in estimation may depend on the existence and quality of studies published. There is a paucity of population-based studies especially in less developed countries and subsequently uncertainty about the burden of CPP.

Reports of *bladder pain syndrome* (BPS) prevalence have great variability because of its controversial clinical diagnosis and the method of screening. Recent reports range from 0.06% to 30% [14–22]. There is a female predominance of about 10:1 [21, 23–25] but possibly no difference in race or ethnicity [26–28]. Vulvodynia rates in BPS patients may vary from 27% to 85%, and it is always higher in case than in control subjects [29, 30]. The relative proportions of classic and non-lesion disease are unclear. There is increasing evidence that also children may be affected; therefore, BPS cannot be excluded on the basis of age [31]. BPS often coexists with other clinical conditions, showing, when compared with controls, greater prevalence of coexisting diagnoses, such as fibromyalgia, chronic fatigue syndrome or irritable bowel syndrome (IBS) [32]. Other authors also showed that women with interstitial cystitis are more likely than controls to be diagnosed with IBS or depression [33].

There is only limited information on the true prevalence of *prostate pain syndrome* (PPS) in the population. As a result of significant overlap of symptoms with other conditions (e.g. benign prostatic enlargement and BPS), purely symptom-based case definitions may not reflect the true prevalence of PPS [27, 34]. In the literature, population-based prevalence of prostatitis symptoms ranges from 1% to 14.2% [35, 36]. 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) [37].

In the 1980s, an association between CPP and sexual dysfunction was postulated. Up to 77% of women with BPS may have deep dyspareunia [38], and up to 25.6% may complain of a complete inability to have sexual intercourse because of pain [39].

In males with PPS the overall prevalence of sexual dysfunction was 49%. Erectile dysfunction (ED) is the most investigated sexual dysfunction in PPS patients. The reported prevalence of ED ranges from 15.1% to 48%, varying with evaluation tools and populations [40, 41]. The prevalence of ED was found to be higher in young men with PPS than in the general population. According to other studies men with

pelvic pain had a higher chance of suffering from ED [42, 43]. Recently, a significant correlation between "chronic prostatitis", CPP symptoms (measured by NIH-CPSI) and ED (measured by International Index of Erectile Function [IIEF]) was confirmed, while other studies using the same questionnaires were not able to confirm such a correlation [44, 45]. Some studies also report ejaculatory dysfunction, mainly premature ejaculation [40, 41, 46, 47].

Screening patients with CPP for myofascial pelvic floor pain or pelvic floor trigger points via interview and physical examination, it was found that 13.2% had pain that was related to the pelvic floor muscles (PFMs) [48].

The prevalence of PFM tenderness in those with other CPP disorders is much higher though. Prevalence of levator ani pain in a CPP clinic over a 7-year period has been found to be 22% [49]. In women with CPP, PFM tenderness was an isolated finding in 15% of these patients but was associated with other CPP disorders in 58.3% of patients versus 4.2% of healthy volunteers. Of the women in the CPP group, 89% had tenderness of the levator ani muscle, 50.8% had tenderness of the piriformis muscle, and 31.7% had tenderness of the internal obturator muscle [50].

Concerning the abdominal aspects of pelvic pain, epidemiological data on IBS and CPP are scarce [51]. The overall prevalence of anorectal pain in a sample of USA householders was 6.6% and was more common in women [52]. IBS is associated with common gynaecologic problems (endometriosis, dyspareunia, and dysmenorrhoea) [53]. Fifty per cent of women who presented with abdominal pain to the gynaecologic clinic or were scheduled for laparoscopy due to CPP had symptoms of IBS [54]. A 40% overlap of IBS in women with CPP was found [55] associated with an increased incidence of somatization. Not gynaecological surgical procedures but only psychosocial variables predict pain development without a different incidence of IBS in a prospective and controlled study [56]. 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 [6].

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Bladder Pain Syndrome/Interstitial Cystitis

5

Mauro Cervigni

5.1 Introduction

According to European/International Society for the Study of Interstitial Cystitis (ESSIC), painful bladder syndrome/interstitial cystitis (PBS/IC) originally described by the International Continence Society (ICS) has recently more precisely defined bladder pain syndrome (BPS/IC) as a syndrome based primarily on symptoms of urgency, frequency, and pain in the bladder and/or pelvis. These collective terms describe debilitating, chronic bladder disorders of unknown causes with an exclusion of confusable diseases. A number of studies have identified the bladder as one of major causes of chronic pelvic pain (CPP) [1–5]. BPS/IC that occur mostly (> 90%) in women is also a disorder of the pelvic floor [6, 7].

Misdiagnosis and ineffective treatments are common, leaving patients with persistent pain and the potential for neuropathic upregulation and allodynia. Currently, BPS/IC is considered a diagnosis of exclusion because its etiology until today is not thoroughly known and clinical characteristics vary among patients. Voiding often relieves the typical symptoms of pain, pressure, or discomfort involving the lower pelvic area including gastrointestinal organs. The symptoms have to be present for no less than 6 months, obviously in the absence of urinary tract infection (UTI). Early recognition of BPS/IC is very important because symptoms are quite disabling, affecting quality of life and leading to patients being seen by a variety of specialists (usually between five and seven times in a period of 3–5 years). The syndrome is also exacerbated by the high incidence of other comorbid diseases including allergies, asthma, atopic dermatitis, inflammatory bowel syndrome (IBS), systemic lupus erythematosus (SLE), Sjögren's syndrome, chronic fatigue syndrome, and fibromyalgia [8–11]. Vulvodynia may also be present in 20% of cases,

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as well as endometriosis in 45–65% of women with pelvic pain of bladder origin [BPS/IC may also be present in men—2.2% of the population using the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)] with less frequent urgency and frequency of urination (type 3 prostatitis, nonbacterial prostatitis, or chronic prostatitis).

5.2 Definition

In 1887, Skene [12] defined the first time "an inflammation that has destroyed the mucous membrane partly or wholly and extended to the muscular parietes". In 1915, Hunner [13] outlined a peculiar form of bladder ulceration whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment in patients with frequency and bladder symptoms.

In 1990, The National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) established a set of consensus criteria, which were developed to ensure the comparability of patients enrolled in clinical studies [14]. These included:

- Hunner's ulcers
- any two of:
  - Pain on bladder filling, relieved by emptying
  - Suprapubic, pelvic, urethral, vaginal, or perineal pain for 9 months
  - Glomerulations on endoscopy or upon hydrodistention under spinal or general anesthesia

However, over 60% of patients with possible BPS/IC appear to fail these criteria expanding the definition [15].

The International Continence Society (ICS) in 2002 defined the term Painful Bladder Syndrome as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as frequency and nocturia in the absence of proven pathologies" [16].

In Kyoto at the ICICJ (International Consultation Interstitial Cystitis Japan) in March 2003, it was agreed that the term "Interstitial Cystitis" should be expanded to "Interstitial Cystitis/Chronic Pelvic Pain Syndrome" when pelvic pain is at least of 3 months duration and associated with no obvious treatable condition/pathology [17].

Most recently, the European/International Society for the Study of Interstitial Cystitis (ESSIC) named this disease Bladder Pain Syndrome [18] according to the definition by the International Association for the Study of Pain (IASP) [19] . According to ESSIC classification score: BPS/IC is indicated by two symbols, the first of which corresponds to cystoscopy with hydrodistention findings (1, 2, or 3, indicating increasing grade of severity) and the second to biopsy (A, B, and C, indicating increasing grade of severity of biopsy findings) (see Table 5.1).

More recently no convincing evidence was found in the reviewed literature that glomerulations should be included in the diagnosis or phenotyping of bladder pain

Table 5.1 ESSIC classification score of bladder pain syndrome (BPS) types

		cystoscopy with hydrodistension			
		not done	normal	glomerulations[1]	Hunner's lesion[2]
biopsy	not done	XX	1X	2X	3X
	normal	XA	1A	2A	3A
	inconclusive	XB	1B	2B	3B
	positive[3]	XC	1C	2C	3C

[1] cystoscopy: glomerulations grade II-III
[2] with or without glomerulations
[3] histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafacicular fibrosis

van de Merwe, J. P., Nordling, J., Bouchelouche, P., Bouchelouche, K., Cervigni et al.: Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol, 53: 60, 2008

syndrome/interstitial cystitis. Glomerulations do not correlate with symptoms and are found in patients without bladder pain syndrome/interstitial cystitis [20]. Therefore, a revisiting of the original classification has been now proposed without glomerulation score (see Table 5.2).

Sometimes a significant proportion of BPS/IC patients do not complain of pain but relate their feelings to pressure and discomfort [21] . In this situation, patients not complaining of pain would remain undiagnosed for IC if only pain syndromes are applicable to a diagnosis of BPS/IC; therefore in May 2009, the Asian Society published clinical guidelines for IC, proposing a new definition of the syndrome as "*Hypersensitive Bladder Syndrome" (HBS)*—bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain [22].

5.3 Epidemiology

The prevalence of BPS/IC is enormously variable according to various authors and studies. The lack of an accepted definition, the absence of a validated diagnostic marker, and questions regarding etiology and pathophysiology make much of the literature difficult to interpret. Overlapping patterns of bladder pain, lower urinary tract symptoms, and pelvic pain are common and present challenges for clinicians and researchers [23] .The other major difficulty in evaluating various prevalence studies is that some are based on unverified self-report, others by physician diagnoses or by identification of BPS symptoms. This confusion becomes apparent when

Table 5.2 ESSIC classification score of bladder pain syndrome (BPS) types revisited

		cystoscopy with hydrodistension		
		not done	normal	Hunner's lesion[2]
biopsy	not done	XX	1X	3X
	normal	XA	1A	3A
	inconclusive	XB	1B	3B
	positive[3]	XC	1C	3C

one looks at the variation in prevalence reports in the United States and around the world. These range from 3.5 per 100,000 population in Japan [24] to 18.1/100,000 women in another epidemiologic study [25]. Subsequent studies in 2002 indicated it was 450 per 100,000 (0.45%), and more recently it was 680 per 100,000 (0.68%) for a probable IC and 300 per 100,000 (0.3%) for a definite diagnosis of IC [26, 27]. A recent study of 981 urban females in Vienna showed an overall prevalence of 306 per 100,000 (0.3%), with the highest number in the 40–59 years age group [28]. BPS/IC has also been reported in children and adolescents [29–31]. Another Japanese study showed the prevalence reported from a questionnaire survey of 300 major hospitals of only 2 per 100,000 patients [32]. The patients were older than those in Europe and the USA [33]. This may indicate that patients have had symptoms for a long time before diagnosis. However, a recent epidemiological investigation in Japan found that 1.0% of the general population experienced bladder pain every day [34]. Estimations of prevalence based on physicians' diagnoses may be thought to produce more accurate estimates. Bade et al. [35] used a physician questionnaire-based survey in the Netherlands yielding an overall prevalence of 8–16 per 100,000 females, with diagnosis heavily dependent on pathology and presence of mast cells. The Nurses Health Study I and II showed a prevalence of IC between 52 and 67 per 100,000 in the USA [36].

In 2000, the European Parliament and the Council of the European Union defined rare diseases (RD) as conditions with a low prevalence threshold (5/10,000 inhabitants in the EC and a high degree of complexity, differently from the rates reported by United States (7.5/10,000) and Japan (4/10,000).

In May 2001 in Italy the Ministry of Health approved a decree to officially establish a very complex national network with reference centers for various diseases with high degree of complexity including RD and a National Registry of Rare Diseases (NRRD) was established. This latter had the objective of collecting data on epidemiology (# of cases and their distribution nationwide) and risk factors. This would help define the size of the problem, estimate the delay in the time to diagnosis and the healthcare migration pattern by patients.

Data were recorded in five significant and the prevalence ranged from 1.9 to 5.1/10,000 (http://malattierare.marionegri.it/images/RRMR_ESENZIONI/2015_12_31_relmar.pdf).

In 2013–2014, NRRD had 1192 patients in a population of almost 61 million. The Italian Prevalence results 1.9 out of 100,000. These results indicate that BPS/IC is not a common occurrence in the Italian population. It is widely agreed that a disease registry is a valuable source of information both for epidemiology and for public health.

It is apparent that there has been no standardized method of determining the prevalence of BPS, with wide variation of estimates in the same study employing different definitions or criteria for identifying the condition. Many factors including bias, cultural differences, methodology, geographic variations in diagnostic criteria, and/or possibly real differences in different populations lead to further variations between countries. There is some evidence of genetic predisposition; the prevalence of BPS/IC in first-degree relatives has been shown to be 17 times higher than in the general population [37].

5.4 Non-bladder Syndromes (NBS)

Over 75% of women with a clinical diagnosis of IC/BPS reported pain outside the pelvis (pelvic pain and beyond) [38].

Multiple observations have shown that BPS patients are more likely than controls to have pain-related syndromes manifesting symptoms beyond the bladder and even the pelvis. Warren et al. [39] demonstrated that significantly more BPS cases than matched controls had 11 antecedent syndromes: fibromyalgia (FM), chronic fatigue syndrome (CFS), inflammatory bladder disease (IBS), sicca syndrome (SS), chronic pelvic pain, migraine, allergies, asthma, depression, panic disorder, and vulvodynia. Nickel et al. [40] found significantly higher prevalence of self-reported FM, CFS, IBS, migraine and tension headaches, vulvodynia, temporomandibular disorder and low back pain in female BPS cases than in controls as well as significantly more with depression and anxiety in a study in several urology practices in three continents [41]. The etiological and epidemiological questions that remain unanswered is how are these NBS associated with BPS, do these NBS precede or follow IC/BPS, and do multiple NBS increase the risk of BPS. Warren et al. [42] have introduced a number of hypotheses; however the studies to validate these have not yet been done. Relatives of BPS patients appear to have an increased risk of associated conditions including myalgia and fibromyalgia as well as constipation,

suggesting shared underlying genetic factors [43]. One other NBS that is sometime neglected or forgotten in these epidemiological associations is the association of BPS with sexual dysfunction. Multiple studies have shown that women with BPS diagnoses or symptoms experience very high levels of sexual dysfunction [44]. This is likely related to deep dyspareunia associated with anterior vaginal wall pain from a hypersensitive bladder but can also be related to vulvodynia, a common NBS seen in female IC/BPS patients [45].

5.5 Etiology and Pathogenesis

Several etiologic theories have been proposed in recent years, although they remain somewhat speculative and controversial, and the precise causes of BPS/IC are still unknown. One aspect has been emphasized: the multifactorial etiology of the disease. Interaction between nervous, immune, and endocrine factors creates a vicious cycle, provoking and maintaining the inflammatory effect in the bladder.

5.5.1 Infection

To date, no infectious etiology has been identified using reverse transcriptase polymerase chain reaction (RT-PCR) for *Chlamydia trachomatis*, adenovirus, cytomegalovirus, herpes simplex virus, papillomavirus, or Gardnerella vaginalis [46, 47]. It is well known that antibiotic treatment is ineffective for BPS/IC. Flare-up of symptoms can occasionally be elicited by an infection, as an associated factor that initiates or exacerbates IC [48].

Recently Siddiqui et al. using 16S ribosomal DNA data demonstrated alterations of microbiota in urine from women with interstitial cystitis [49]. Using culture-independent method to compare the microbiota of the lower urinary tract in standard culture negative (for bacteria) female patient with BPS, Nickel et al. showed that among women with BPS the prevalence of fungi (Candida and Saccharomyces sp.) was significantly greater in those who reported a flare compared to those who did not [50]. Nevertheless, the possibility of a microbial contribution to the etiology of BPS remains an open question.

5.5.2 Mastocytosis

An increased number of activated bladder mast cells has been reported repeatedly in BPS/IC [51]. There are twice as many mast cells in the urothelium of BPS/IC patients and ten times more in the detrusor as compared to controls [52]. In addition, more than 70% of bladder mast cells were activated in BPS/IC as compared to less than 10% in controls. In fact the mast cells play a pivotal role in the inflammatory process: they release potent inflammatory mediators such as histamine, leukotriene,

and serotonin, and also interact with immunoglobulin E (IgE) antibodies, other inflammatory cells, and the nervous system [53].

There is a significant increase in mast cell count in subepithelial region from BPS patients with Hunner lesions as compared to non-Hunner lesion BPS patients or patients with overactive bladder syndrome [54, 55]. Recent studies raise doubt about whether mast cell counts are adequately informative to evaluate BPS/IC. In pats. with or without Hunner lesions the lymphocyte infiltration and urothelium integrity could be superior histopathological criteria**.** Moreover density of the mast cells alone was not able to differentiate BPS/IC without Hunner's lesion from OAB [56]. In conclusion, the mast cell count is of no value in the differential diagnosis between IC and other etiologies**.** The mast cell count is of no value in the differential diagnosis between IC and other etiologies. ...Another piece of "uromythology" has been demolished [57].

5.5.3 Dysfunctional Bladder Epithelium

The protective inner layer of the bladder is made up of glycosaminoglycans (GAGs), chondroitin sulfate (CS), and sodium hyaluronate (SH). This GAG component is hydrophilic and binds a layer of water molecules that is thought to protect the urothelium from potentially harmful agents, including bacteria, proteins, and ions. Proponents of the leaky endothelium theory suggest that the GAG layer may be damaged in BPS/IC [58, 59]; this deficiency allows irritants in the urine to leak through the urothelium and causes inflammation, irritation, and numerous other reactions [60].

Increased urinary levels of CS and SH have been reported in some BPS/IC patients [61, 62], with concomitant decrease of mucosal glycoprotein GP1 [63].

Zhang et al. [64] demonstrated significantly increased paracellular permeability, decreased expression of the tight junction proteins ZO-1 and occludin, and increased expression of the adhesion protein E-cadherin from patients with BPS. Shie et al. [65] further showed that in the urothelium of the BPS bladder a reduced E-cadherin expression was associated with a higher level of apoptosis.

The etiology of the defect in the GAG layer is currently unknown. Antiproliferative factors (APFs), detected in the urine of IC patients, downregulate expression of genes that stimulate proliferation of bladder epithelial cells, and upregulate genes that inhibit proliferation, leading to urothelial undermaturation and dysfunction [66, 67].

5.5.4 Neurogenic Inflammation

BPS/IC is not an end-organ condition; it should be considered a condition of the peripheral and central nervous systems as they relate to acute or chronic pain. The initiating event is a noxious stimulus such as trauma, infection, or inflammation. Acute pain is associated with nociception, which results in pain perception modulated in the peripheral and central nervous systems. Conversion of acute to chronic

pain begins with activation of visceral silent unmyelinated C-fibers by prolonged noxious stimulation and inflammation. The neurotransmitter glutamate is released, which activates N-methyl-d-aspartate receptors. A chronic pain cycle begins as dorsal horn neurons are activated (wind-up), which causes exaggerated responses to less noxious stimuli (hyperalgesia), or a painful response to normally innocuous stimuli (allodynia), as small volumes of urine in the bladder are perceived as a full bladder. The neurotransmitter substance P stimulates the release of histamine and nitric oxide, which causes neurogenic inflammation. Once the dorsal horn becomes hypersensitive, the pain syndrome becomes a chronic pain syndrome. Prolonged noxious stimuli can cause dorsal horn cells to transmit efferent signals to peripheral nerve terminals (antidromic transmission). Thus, a self-perpetuating signal is established as a visceral CPPS, causing expression of genes such as c-Fos in the spinal cord and loss of inhibitory neurons, resulting in a decreased threshold for activation. Akiyama et al. [68] have demonstrated in innovative animal studies that there is a bidirectional neural cross-sensitization of the colon and lower urinary tract. Acute colitis sensitized lumbosacral spinal neurons receiving input from the urinary bladder result in spinal neuronal hyperexcitability that may be involved in central cross-organ sensitization of visceral nociception between the colon and urinary bladder. This provides information which not only supports a neurogenic etiology but also may account for the substantial overlap of BPS with other chronic pelvic pain disorders, especially the inflammatory bowel disorders [69]. The brain might also play a role in the neurobiological component of BPS/IC. Using contrast-enhanced magnetic resonance imaging, Kairys et al. [70] showed an increased brain gray matter in the primary somatosensory cortex associated with increased pain and mood disturbance in patients with BPS.

5.5.5 Reduced Vascularization

A decrease in the microvascular density has been observed in the suburothelium in patients with BPS/IC [71]. Bladder vascular perfusion is reduced by bladder filling in BPS/IC, while it is slightly increased in controls [72].

A recent paper showed that hyperbaric therapy seems to relieve the symptoms of BPS/IC [73], confirming indirectly that a reduced blood supply may cause a decrease in epithelial function as well as epithelial thinning and denudation [74]. It is reasonable that the impaired blood circulation in the bladder is related to BPS/IC and the apoptotic activity of microvascular endothelial cells is increased [75].

5.5.6 Pelvic Floor Dysfunction

Many patients with bladder painful syndrome/interstitial cystitis (BPS/IC) have concomitant pelvic floor dysfunction (PFD), with muscle tenderness and spasm also known as hypertonic pelvic floor dysfunction (HPFD). Previous studies found that myofascial pain and HPFD are present in as many as 85% of patients with BPS/IC and/or chronic pelvic pain (CPP) syndrome [76]. Probably is the same or very

similar to Category IIIB chronic prostatitis/chronic pelvic pain syndrome (CP/CCPS) in male population [77, 78].

Inflammatory or pain disorders of pelvic viscera, a trauma, or an abnormal behavior may elicit noxious stimuli to sacral cord that set up a pelvic floor muscle dysfunction with sacral nerve hypersensitivity and a sacral cord wind-up [79–83].

The "Guarding Reflex" is a viscero-muscular reflex activated with the aim to increase the tone of the pelvic floor during routine daytime activity [84].

In BPS/IC patients there is an afferent autonomic bombardment that may enhance and maintain a guarding reflex that manifests itself as a hypertonus of the pelvic floor. On the other hand, vulvodynia, dyspareunia, scrotal and perineal pain are one of the expressions of the exaggerated muscle tone activity, contributing to the maintenance of the noxious stimuli. Approximately 15% present with pain as the only symptom [85].

5.5.7 Autoimmunity

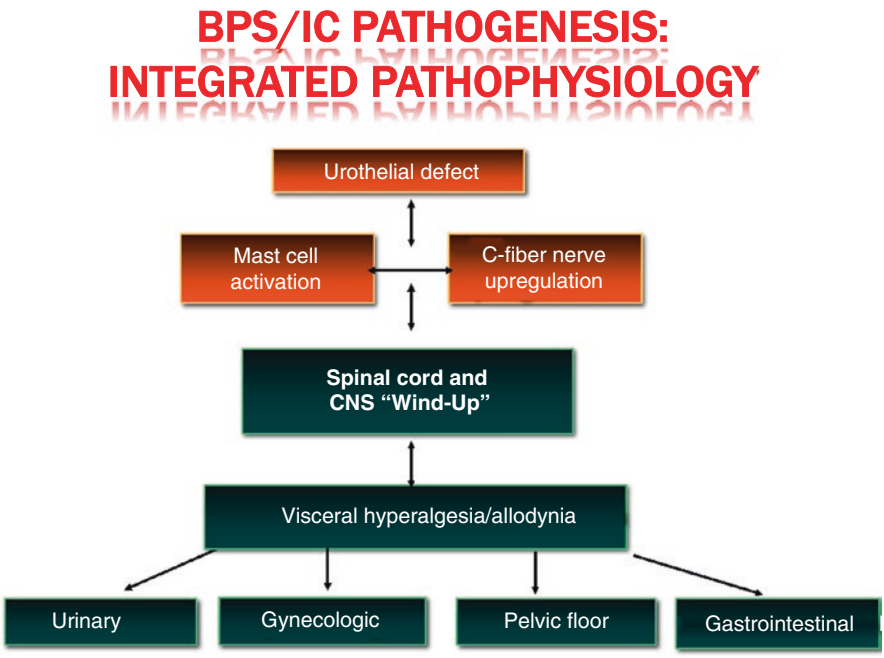
Many of the clinical features of BPS/IC reflect an autoimmune component of the disease process. Investigators have also reported concomitant association of BPS/IC and other autoimmune diseases, such as SLE, rheumatoid arthritis, and Sjögren's syndrome [86–88]. There are numerous reports on autoantibodies in patients with BPS [87, 89]. The precise identity of these autoantibodies has yet to be determined. Some of the common clinical and histopathological characteristics present in BPS patients show certain similarities with other known autoimmune disturbances. Studies on autoantibodies in BPS have shown that these mainly consist of antinuclear antibodies and these findings are in turn similar to the autoantibody profiles in some systemic diseases [89, 90], Table 5.3 summarizes the integrated pathophysiology of the syndrome in a schematic way.

5.6 Diagnosis

It is important to keep in mind that BPS/IC patients may present with only one of the symptoms, particularly early in the course of the disease. Up to 30% with BPS/IC present without pelvic pain [91], and approximately 15% present with pain as the only symptom [85].

The diagnosis of BPS/IC is symptom driven by exclusion, but should not necessarily be organ oriented, considering the large number of confusable diseases (Table 5.4). A comprehensive medical history should include suprapubic pain, pressure, and discomfort related to bladder filling, as well as frequency and urgency in the absence of UTI or other pathology [92]. A retrospective analysis from the IC Database (ICDB) pointed out that the most common baseline pain site was lower abdominal (80%), urethral (74%), and low back (65%), with the majority of patients describing their pain as intermittent [93].

Table 5.3 BPS/IC pathogenesis: integrated pathophysiology



Questionnaires can be helpful in screening for BPS/IC. The most commonly used screening tools are the Pelvic Pain, Urgency, Frequency symptom scale (PUF)) and O'Leary–Sant Symptom and Problem Index [94, 95] (Fig. 5.1). Both surveys include questions regarding pain, urgency, frequency, and nocturia and how these symptoms impact on quality of life.

Physical evaluation is a critical component of diagnosing BPS/IC. Since the bladder is a pain generator, tenderness with single-digit examination of the trigonal area can help establish a diagnosis of BPS/IC [96] as pelvic floor tenderness at the trigger point in the levator muscles [97]. Physical examination should also address high tone of the pelvic floor muscles, and hypersensitivity of the perineal area using the Kaufman Q-Tip touch sensitivity test that might screen for the presence of vulvodynia (VS) [98]. Urine analysis can rule out hematuria, and urine culture is required to identify bladder infection as cytology can help rule out bladder cancer. Several optional diagnostic tests are also used but diagnostic evaluation varies among urologists/urogynecologists, in different centers [99–101] and between the USA, Europe, and Asia. Intravesical administration of 40 mL of a solution of 40 mEq of potassium chloride in 100 mL of water (potassium sensitivity test—PST) with pain and urgency scored by the patient as compared to administration of sterile water has been proposed for BPS/IC diagnosis. However, this test's sensitivity and specificity is only about 75% and the participants at the International IC Consultation

Table 5.4 Differential diagnosis of bladder pain syndrome: confusable diseases

Carcinoma and carcinoma in situ	Cystoscopy and biopsy
Infection with	
Common intestinal bacteria	Routine bacterial culture
Chlamydia trachomatis, Ureaplasma urealyricum	Special cultures
Mycoplasma hominis, Mycoplasma genitalium	
Corynebacterium urealyticum, Candida species	
Mycobacterium tuberculosis	Dipstick; if "sterile" pyuria culture for *M. tuberculosis*
Herpes simplex and human papilloma virus	Physical examination
Radiation	Medical history
Chemotherapy, including immunotherapy with cyclophosphamide	Medical history
Anti-inflammatory therapy with tiaprofenic acid	Medical history
Bladder-neck obstruction and neurogenic outlet obstruction	Uroflowmetry and ultrasound
Bladder stone	Imaging or cystoscopy
Lower ureteric stone	Medical history and/or hematuria: upper urinary tract imaging such CT or IVP
Urethral diverticulum	Medical history and physical examination
Urogenital prolapse	Medical history and physical examination
Endometriosis	Medical history and physical examination
Vaginal candidiasis	Medical history and physical examination
Cervical, uterine, and ovarian cancer	Physical examination
Incomplete bladder emptying (retention)	Postvoid residual urine volume measured by ultrasound scanning
Overactive bladder	Medical history and urodynamics
Prostate cancer	Physical examination and PSA
Benign prostatic obstruction	Uroflowmetry and pressure-flow studies
Chronic bacterial prostatitis	Medical history, physical examination, culture
Chronic non-bacterial prostatitis	Medical history, physical examination, culture
Pudendal nerve entrapment	Medical history, physical examination, nerve block may prove diagnosis
Pelvic floor muscle-related pain	Medical histroy, physical examination

Van de Merwe J, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK et al. Diagnostic criteria, classification, and nomenclature for Painful Bladder Syndrome/Interstitial Cystitis: An ESSIC proposal. Eur. Urol. 2008;53:60

	0	1	2	3	4	Symptom score	Bother score
1. How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
b. If you get up at night to go to the bathroom, does it bother you?	Never	Occasionally	Usually	Always			
3. Are you currently sexually active? YES _____ NO _____							
4a. IF YOU ARE SEXUALLY ACTIVE, do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Occasionally	Usually	Always			
b. If you have pain, does it make you avoid sexual intercourse?	Never	Occasionally	Usually	Always			
5. Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, testes, or scrotum)?	Never	Occasionally	Usually	Always			
6. Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always			
7a. If you have pain is it usually		Mild	Moderate	Severe			
b. Does your pain bother you?	Never	Occasionally	Usually	Always			
8a. If you have urgency, is it usually		Mild	Moderate	Severe			
b. Does your urgency bother you?	Never	Occasionally	Usually	Always			

Fig. 5.1 Questionnaires: Pelvic Pain, Urgency, Frequency Scale (PUF)

in Rome recommended that it should not be used for diagnostic purposes because of its low prognostic value [102].

5.7 O'Leary Sant Symptom and Pain Index

Interstitial Cystitis Symptoms Index During the past month:

How often have you felt the strong need to urinate with little or no warning:
0. __ Not at all
1. __ Less than 1 time in 5
2. __ Less than half the time
3. __ About half the time
4. __ More than half the time
5. __ Almost always

Have you had to urinate less than 2 hours after you finished urinating?
0. __ Not at all
1. __ Less than 1 time in 5
2. __ Less than half the time
3. __ About half the time
4. __ More than half the time
5. __ Almost always

Interstitial Cystitis Symptoms Index During the past month:

How often did you most typically get up at night to urinate?
0. __ Not at all
1. __ Once per night
2. __ 2 times per night
3. __ 3 times per night
4. __ 4 times per night
5. __ 5 or more times per night

Have you experienced pain or burning in your bladder?
0. __ Not at all
1. __ A few times
2. __ Fairly often
3. __ Usually
4. __ Almost always

Add the numerical values of the checked entries:
Total score

Interstitial Cystitis Problem Index During the past month how much has each of the following been a problem for you.
Frequent urination during the day?
0. __ No problem
1. __ Very amall problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem

Getting up to at night to urinate?

0. __ No problem
1. __ Very amall problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem Need to urinate with little warning?

Interstitial Cystitis Problem Index During the past month how much has each of the following been a problem for you.
Need to urinate with little warning?
0. __ No problem
1. __ Very amall problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem

Burning, pain, discomfort, or pressure in your bladder?
0. __ No problem
1. __ Very amall problem
2. __ Small problem
3. __ Medium problem
4. __ Big problem

Add the numerical values of the checked entries:
Total score

Urodynamic studies can highlight detrusor overactivity or reduced bladder capacity without detrusor overactivity (bladder hypersensitivity) suggestive of BPS/IC [103–105]. A mild impaired voiding phase with detrusor-sphincter discoordination is probably related to the dysfunctional pelvic floor behavior. In females, flowmetry, post-void residual urine volume and pressure-flow study are optional. In males, a flowmetry should be done in all, and if maximum flow rate <20 mL/s a pressure-flow study and measure of residual urine volume should be done. It is recommended to perform filling cystometry with a filling rate of 50 ml/s to look for overactivity, volume at first desire to void and cystometric capacity. A revised Potassium Test can be performed using cystometric capacity and a 0.2 M KCL solution. The so-called revised or Comparative Potassium Test (according to Daha et al.) has shown prognostic value in bladder irrigation studies [106] but is considered optional by ESSIC.

Local cystoscopy is not mandatory but is a good preliminary investigation to rule out other conditions (e.g., bladder stone, hematuria, or cancer)**.** Cystoscopy is also needed to identify Hunner's lesions [107], the positive specific finding of BPS/IC. Typically, an ulcer is recognized as a well-demarcated reddish mucosal lesion lacking the normal capillary structure and sometimes with a spontaneous bleeding during inspection. In addition, some scars or fissures with a rich

hypervascularization or a pale mucosal aspect may be found, and are an indirect index of hypovascularization.

Cystoscopy with hydrodistention under anesthesia is proposed by the NIDDK research criteria, but is now considered too restrictive [101]; however, it remains the most common procedure performed in patients with BPS/IC especially in Europe [108]. Hydrodistention is also done using different methodologies, making comparison between studies difficult [98, 109, 110]. It may be necessary to exclude other pathologies and to identify the presence of "classic" BPS/IC with "Hunner's lesions," and document urothelial bleeding (glomerulations), even though these have also been noted in the bladders of normal women undergoing tubal ligation [111].

Bladder biopsy has to be performed after hydrodistention to avoid the risk of bladder rupture, to prove the presence of mast cell infiltration, and to orientate toward a more specific therapy. Biopsy with histopathology may be necessary to exclude neoplasm and eosinophilic or tuberculosis cystitis. A count of tryptase-positive bladder mast cells is recommended by the European Society, with >28 mast cells/mm constituting detrusor mastocytosis, which is considered diagnostic for BPS/IC [101, 109, 112]. An increased number of mast cells was also recently proposed as a diagnostic criterion for vulvodynia syndrome [113].

There are no specific blood or urine markers available for diagnosis. A major factor affecting the controversy over accepted clinical diagnostic criteria is that the current criteria are predominantly symptom specific. An objective biomarker would advance the establishment of reproducible diagnostic criteria for BPS and also aid in monitoring effects of treatment. A biomarker for any disease needs to demonstrate high sensitivity and high specificity. An AntiProliferative Factor (APF), recently identified as a frizzled-8 surface sialoglycopeptide [114], was increased in BPS/IC urine as determined by its ability to decrease in vitro proliferation of bladder epithelial cells, and could distinguish BPS/IC from other urologic disorders [115] . Urine APF levels also apparently distinguished BPS/IC from CPPS in men [116]. However, APF still needs to be validated and independently reproduced. Classic BPS/IC might be differentiated from nonulcer disease by elevated urine nitric oxide (NO) [117]. GP-51 is a glycoprotein present in both the transitional epithelium and urine of humans and other mammals. Moskowitz et al. have shown that bladder biopsies of BPS patients had decreased staining for GP-51 [118]. The same laboratory also demonstrated that although GP-51 demonstrates a high specificity for BPS, it is not as sensitive as APF [119].

5.8 Gynecological Associated/Confusable Disease

In female population affected by BPS/IC the gynecological pathologies may be present in about 20% of pats. and there is also an overlapping of musculoskeletal pathologies in 12% of cases [120].

The associated pathologies are:

(a) *Pelvic floor dysfunction:* affects the anterior, apical, or posterior vaginal compartment with muscle tenderness, spasms, and voiding dysfunction, both manifestations of pelvic floor hypertonicity [76]. It has been estimated that the prevalence of HPFD in patients with BPS/IC ranges from 50% to 87% [121]. Pelvic floor dysfunction exacerbates BPS/IC symptoms, and has been reported to appear in response to events such as bladder inflammation, gait disturbance, and trauma [122].

(b) *Endometriosis:* is the presence of endometrial glands or stroma outside of the endometrial cavity and affects 1–7% of the general population [123]. Up to 70% of women with endometriosis have some type of pain symptoms, most commonly dysmenorrhea, cyclic pelvic pain, or deep dyspareunia. In women who undergo a laparoscopy to evaluate CPP, the prevalence of endometriosis is 30–90% [124]. There is a high prevalence and association of IC and endometriosis. A study by Chung et al. of 178 women with CPP found that 65% of CPP patients suffered from both active endometriosis and IC [125]. A recent systematic review estimated the prevalence of BPS/ IC, and the coexistence of BPS/IC and endometriosis in women with CPP. Nine studies including 1016 patients with CPP showed the mean prevalence of BPS was 61%, of endometriosis 70%, and coexisting BPS and endometriosis 48%. These data suggest the importance of considering the bladder as the source of pain even where endometriosis is confirmed, and in the case of unresolved endometriosis and persistent pelvic pain, patients must be evaluated to rule out the presence of BPS/IC [126].

(c) *Vulvodynia:* also known as vulvar vestibulitis or vulvar dysesthesia syndrome, literally means pain, or an unpleasant altered sensation, in the vulva. Pain can be unprovoked, varying from constant to intermittent, or occurring only on provocation, such in sexual intercourse. Peters et al. reported that vestibulodynia affects 25% of women with BPS/IC [127]. The etiology of vulvodynia is presumed to involve many factors: infections and altered vaginal acid-base balance, and the upregulation of pro-inflammatory immune responses. Furthermore, a large community-based study found that vulvodynia was strongly associated with childhood physical or sexual abuse [128].

(d) *Pudendal neuropathy:* is a common feature of syndromes such as dysfunctional voiding, nonobstructive urinary retention, chronic pelvic pain syndromes, and urinary and fecal incontinence. It could be ruled out as a confusable disease in BPS/IC patients. Pudendal neuralgia is a functional entrapment of the pudendal nerve, and pain occurs during compression or stretch maneuvers, such as repetitive microtrauma, fracture, straining with constipation and childbirth, falls onto the buttocks, and suture entrapment during pelvic surgery. The main symptom is pain aggravated by sitting/driving/exercise, reduced by recumbence or standing, and relieved by sitting on a toilet. The quality of neuropathic pain varies, and can be induced by voiding, defecating, vaginal penetration, or orgasm. It can occur in the perineum and urethra, and extends to suprapubic, inguinal regions and to the upper medial thighs. Urinary symptoms and rectal dysfunction might occur. Sexual dysfunction could be present [129]. In women affected by BPS/IC is mandatory to observe not only the bladder, but also the other

components responsible for the pain disorder. Patients with bladder tenderness alone responded better than patients with multiple tender trigger points, possibly because in these patients the bladder is the only target organ and the patients are less severely affected than patients with multiple trigger points. Multimodal therapy remains the gold standard in the management of female BPS/IC patients.

5.9 Treatment

There is no curative therapy for BPS/IC [130–133]. This is consistent with the fact that the causes of BPS/IC are yet not understood and the pathophysiology remains uncertain.

Therefore, the therapeutic strategy is to reduce or eliminate the symptoms of BPS/IC, thereby interfering with the potential disease mechanism and improving quality of life.

Because IC is a chronic disease, patients should be counselled regarding realistic expectation of treatment. Remission may be attained but should not be expected, and even when it is attainable, months of medical treatment may be required [134]. Exacerbations during periods of remission are common.

5.10 Multimodal Medical Therapy

To manage the multiple pathological features of IC, a multimodal approach, combining agents from different classes, is suggested to improve the therapeutic response by attacking the disease at several points. One common multimodal approach is:

1. To restore epithelial function with heparinoid
2. To treat neural activation and pain with TriCyclic Antidepressants (TCA)
3. To control allergies with an antihistamine

In advanced form, intravesical treatment may be required. Combination intravesical therapy is also indicated for patients who experience significant flare of symptoms after remission.

5.10.1 First Line: Conservative Therapy

Behavioral modification including education, timed voiding (scheduled voiding time and interval), controlled fluid intake, pelvic floor muscle training, and bladder training (gradually extending voiding interval) may have modest benefit for IC patients (grade of recommendation B). It is believed that exercise and bathing

favorably influence the quality of life by reducing stress; however, the effect of such nonspecific therapies are difficult to assess and have not been proven in clinical trials. It would seem reasonable to suggest, when possible, to shorten working hours, choose a job with less stress, or create a less stressful home environment. Involvement in patient education programs and patient support groups are considered by most practitioners to be beneficial [135]. Barbalias et al. [136] looked at a type of bladder training as an adjunct to treatment with intravesical oxybutynin in patients with IC; there was a modest improvement in O'Leary–Sant questionnaire at 6 months. Chaiken et al. [137] reported similar results with diary-timed voiding and pelvic floor muscle training. There are no randomized controlled trials (RCTs) attesting the efficacy of pelvic floor physical therapy. Biofeedback and soft tissue massage may aid in muscle relaxation of the pelvic floor [138].

Manual physical therapy (grade of recommendation C) to the pelvic floor myofascial trigger points twice per week for 8–12 weeks also resulted in moderate to marked improvement in 7/10 BPS/IC patients [139].

Modified Thiele intravaginal massage of high-tone pelvic floor muscle trigger points twice per week for 5 weeks has been shown to improve the O'Leary–Sant Index [140].

Common-sense dietary changes, especially avoidance of potential bladder irritancy as identified by individual patients, may be beneficial (grade of recommendation B).

A majority of BPS/IC patients seem to have symptom exacerbation related to the intake of specific foods and beverages: coffee, spicy foods, and alcoholic beverages [141].

However, different patients seem to be affected to different degrees by specific foods and beverages and patients should avoid only those foods and beverages that they find worsen their symptoms.

5.10.2 Second Line: Medical Therapy

Medical therapies for BPS/IC include oral, subcutaneous, and intravesical agents. These drugs are categorized according to their intended point of action within the disease process.

5.11 Oral Therapy

5.11.1 Pain Modulators

The long-term, appropriate use of pain medications is one of the main steps in the treatment of BPS/IC. Many nonopioid analgesics and the nonsteroidal anti-inflammatory drugs (NSAIDs) and even antispasmodic agents have a place in pain therapy.

5.11.2 Analgesics (Grade of Recommendation: C—Level of Evidence: 4)

Gabapentin, introduced as an anticonvulsant, has found efficacy in neuropathic pain disorders and it demonstrates synergism with morphine in neuropathic pain [142]. Sasaki et al. reported that 10 of 21 male and female patients with refractory genitourinary pain had subjective improvement of their pain following treatment with gabapentin [143].

Pregabalin has similar structure as gabapentin and might be worthwhile to try for bladder pain syndrome, particularly for those with concurrent fibromyalgia, though studies are lacking [144]. *Opioids* are seldom the first choice of analgesics in chronic pain states, if less powerful analgesics have failed [145]. Chronic opioid therapy can be considered as a last resort in selected patients, who have disabling pain and often receive inadequate doses of short-acting pain medications. The major impediment to the proper use of opioids when they are prescribed for long-term nonmalignant pain is the fear of addiction. In addition to narcotics, concurrent usage of nonsteroidal anti-inflammatory drugs, cyclooxygenase inhibitors, acetaminophen, and tricyclic antidepressants may provide better pain control [146]. The common side effects of opioids include sedation, nausea, and mild confusion. Constipation is common and a mild laxative is generally necessary.

5.11.2.1 Tricyclic Antidepressants(TCAs)

Amitriptyline is known to have pain-reducing effects (grade of recommendation B, level of evidence 2). One recent RCT of amitriptyline evaluated 50 patients with IC. Improvement in overall symptom scores was significantly greater in the treatment group, as well reduction in pain and urgency ($P < 0.001$). van Ophoven et al. performed the first prospective, double-blind, placebo-controlled study of amitriptyline. Fifty patients were randomized to placebo. 42% patients had greater than 30% decrease in O'Leary/Sant symptom and problem scores at 4 months compared to 13% in the placebo group. They subsequently reported a long-term follow-up of amitriptyline for patients who can tolerate the side effects and continued the medication. With a mean follow-up of 19 months, 64% of 94 patients had response [147]. Foster and Hanno [148] reported a second multicenter, RCT double-blind placebo controlled of amitriptyline in subjects with BPS/IC. Only of the subgroup of 207 subjects who achieved a drug dose of at least 50 mg, a significantly higher response rate was observed in the amitriptyline group (66%) compared to placebo (47%) ($P = 0.01$).

Doxepin, Desipramine, Duloxetine

Other tricyclic antidepressants that have been used for bladder pain syndrome are doxepin and desipramine. Wammack et al. used the combination of doxepin and piroxicam, a cox-2 inhibitor. Twenty-six of 32 patients (81%) experienced remission of symptoms [149]. One study reported satisfactory outcome with desipramine [150]. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, has also been tried but without therapeutic effects [151].

5.11.3 Protection of the Mucosal Surface

One of the theories in the pathogenesis of IC is that deficiency of the GAG layer causes symptoms related to the increased permeability of the urothelium. Therefore, a number of agents have been used to improve the integrity of the mucosal surface.

- Pentosan polysulfate (PPS), a branched polysaccharide presumably acting to "replenish" the GAG layer, is the only oral drug approved in the USA for BPS/IC (grade of recommendation B, level of evidence 2). One study of PPS (300 mg/day) used for 3 years showed it was twice as potent as placebo (18%) in reducing pain but the placebo response was unusually low. A randomized double-blind multicenter study, with a range of doses (300, 600 or 900 mg/day) for 32 months, of 380 BPS/IC patients with >6 months' symptoms and positive cystoscopic examination but no placebo control, reported that 45–50% of all patients were classified as responders (50% or greater improvement on the Patients' Overall Rating of Symptoms Index—PORIS), irrespective of the dose [152]. In a recent prospective study, 41 patients with BPS/IC were divided into three groups according to their response to PPS (major, intermediate, minor); they were administered 3 × 5000 IU subcutaneous heparin per day for 2 days, followed by 2 × 5000 IU per day for 12 days plus 300 mg PPS per day, compared to 17 nonmatched patients taking PPS alone; 32% of the patients in the minor response group reported a significant improvement in "overall well-being" over that of PPS alone [153].

5.11.3.1 Antihistamines

Simmons first proposed use of antihistamines in 1955 [154]. His findings of mast cells in the wall of a normal bladder and the edema and increased vascularity seen in the IC bladder suggested that histamine may be responsible for the development of interstitial cystitis.

- *Hydroxyzine* is a histamine1 receptor antagonist, with additional anxiolytic, sedative, anticholinergic, and mast cell inhibitory properties (grade of recommendation D, level of evidence 1). It has been shown to reduce neurogenic bladder inflammation [155]. Hydroxyzine has shown mixed results in treating BPS/IC symptoms. One open-label study showed a 55% reduction in symptoms, particularly in patients who suffered from allergies [156].
- *Cimetidine* is a histamine-2 receptor antagonist (grade of recommendation D, level of evidence 4). It was reported to decrease the median symptom score in 34 BPS/IC patients studied, but with no apparent histological changes in the bladder mucosa [157].

5.11.3.2 Immunosuppressant

- *Cyclosporine*
  Cyclosporine, a widely used immunosuppressive drug in organ transplantation, has been used in a longer-term follow-up study, on refractory IC patients and it was considered far superior to sodium pentosanpolysulfate in all clinical out-

come parameters measured at 6 months. Patients who responded to cyclosporine A had a significant reduction of urinary levels of epidermal growth factor (EGF) [158]. Forrest et al. [159] retrospectively summarized results from Cyclosporine off-label use in 44 BPS patients. In 34 patients presenting with Hunner's lesion upon cystoscopy the success rate was higher compared to those patients without lesions (68% vs 30%). However, side effects were common and demand a close monitoring of patients including blood pressure and renal failure.

- *Suplatast*
  Tosilate Suplatast Tosilate (IPD-1151 T) is an immune regulator that selectively suppresses IgE production and eosinophilia via suppression of helper T cells that produce IL-4 and 5. Ueda et al. reported a small study in 14 women with interstitial cystitis [160]. Treatment for 1 year resulted in a significantly increased bladder capacity and decreased urinary urgency, frequency, and lower abdominal pain in 10 women. Larger, multicenter international RCTs have been completed and results did not justify further development for this indication.
- *Corticosteroids*
  Reports on outcome with corticosteroid therapy have been both promising and discouraging [161]. The side effects of steroids can be very serious, making it difficult to justify their use [162, 163].

5.11.3.3 Other Oral Medications

- *l-Arginine*
  It is a natural substrate of nitric oxide synthase (NOS) (grade of recommendation D). It may reactivate NOS activity, which is suppressed in IC, and relieve symptoms [164]. No significant effect was observed in double-blind studies [165, 166].
- *Quercetin*
  Quercetin is a bioflavonoid that has an anti-inflammatory effect and is found in fruits, vegetables, and some spices. In a small study of 22 BPS patients followed for 4 weeks, all but one patient had some improvement in the O'Leary/Sant symptom and problem scores as well as in a global assessment score. Further studies are necessary to determine efficacy [167].
- *Sildenafil*
  The contraction of smooth muscle caused by elevating potassium or adrenergic activity can be relaxed by phosphodiesterase type 5 inhibitors (a class of drugs approved to treat erectile dysfunction). Forty-eight women with a clinical diagnosis of BPS were randomly assigned to treatment or placebo for 3 months [168]. The O'Leary-Sant IC symptom and problem indices, VAS, and a micturition diary were recorded before treatment, and after the treatment until 3 months. The IC symptom and problem indices scores and urodynamic index were significantly improved in sildenafil treatment group as compared with placebo group and baselines ($P < 0.05$). The efficiency of treatment reached 62.5%. The adverse events were mild to moderate and transient. The mode of action of sildenafil in BPS remains unclear. Further larger studies are necessary to confirm the results of this innovative study. More detailed results of the use of oral drugs in BPS/IC patients is shown in Table 5.5.

Table 5.5 Oral medications for treatment of BPS/IC

Drug	RCT	GoE: LR
Gabapentin	No	C: 4
Pregabalin	No	C: 4
Amitriptyline; tricyclic antidepressant	Yes	B: 2
PPS	Yes	D: 1
Hydroxyzine	Yes	D: 1
Cimetidine	Yes	C: 3
Ciclosporin	No	C: 3
Suplatast tosilate	No	D: 3
Hydrocortisone	No	Ineffective
l-Arginine	Yes	A: 1
Quercetin	No	D: 4
Sildenafil	No	D: 1

GoE Grade of Evidence, *LR* Level Recommendation

5.12 Intravesical Instillation or Bladder Wall Injection

Heparin intravesically and subcutaneously has been used for the treatment of IC since early 1960. It is either instilled or administered subcutaneously. When instilled, heparin does not have systemic anticoagulant effects. In one study, 48 patients with IC self-administered intravesical heparin (10,000 IU in 10 mL sterile water 3 times weekly for 3 months). Fifty-six per cent of the patients attained clinical remission after 3 months. Subcutaneous heparin has been demonstrated to produce rapid relief of symptoms in eight patients, who reported long-term benefit over 1 year [169].

- *Intravesical dimethylsulfoxide (DMSO)* remains the basis of intravesical therapy for IC (grade of recommendation B, level of evidence 2). It has been shown to reduce symptoms for up to 3 months. Its multiple effects include an anti-inflammatory and analgesic effect, muscle relaxation, mast cell inhibition, and collagen dissolution [170]. Patients treated with DMSO have experienced a 50–70% reduction of symptoms, although the relapse rate is 35–40%. Administration in combination with various other agents including hydrocortisone, heparin, and sodium bicarbonate has been recommended to improve the response to DMSO.
- *Intravesical hyaluronic acid* (grade of recommendation C, level of evidence 1) has been used with a long-lasting moderate efficacy with no side effects, but a RCT performed by Bioniche Company reported no significant efficacy of their preparation (40 or 200 mg per cc respectively) and neither showed significant efficacy of sodium hyaluronate compared to placebo in large phase 3 trials. These negative studies have not been published in peer-reviewed literature (http://www.medicalnewstoday.com/articles/112053.php). Neither preparation has been approved for use for BPS in the USA.

- *Chondroitin sulfate* (grade of recommendation C, level of evidence 1). Steinhoff et al. treated 18 patients with 40 mL intravesical Chondroitin: 46.2% showed a good response, 38.5% had a partial or no response [171]. In 2013, a larger and long-term studies was made on 213 patients. At the end of the treatment GRA rates were 43.2% in the chondroitin group and 27.4% in the control group and the chance of having becoming a responder with chondroitin sulfate was 55% significantly higher than with placebo. The small decrease in total score and urine frequency between the two groups was less impressive and not statistically significant.
- *Combined instillation of hyaluronic acid and chondroitin sulfate* (Grade of Recommendation: C, Level of Evidence: 2).

Recently Cervigni et al. [172] published a randomized, open-label, multicenter study involving 110 women randomized to receive 13 weekly instillations of HA (1.6%—800 mg) and CS (2.0%—1 g) (Ialuril®; IBSA) or 50% DMSO solution (RIMSO®; Bioniche), with a 2:1 allocation ratio. This study showed that treatment with HA/CS appears to be as effective as DMSO with a potentially more favorable safety profile. Both treatments increased health-related quality of life, while HA/CS showed a more acceptable cost-effectiveness profile.

Pentosan polysulfate (PPS) is a mucopolysaccharide similar to heparin, with a similar postulated mode of action when used locally. Like other mucopolysaccharides, it has not been well studied clinically. A randomized controlled trial found benefit in 4 patients out of 10 on PPS versus 2 of 10 on placebo [173]. A placebo-controlled study of 41 patients found the addition of a 6 week course of intravesical PPS to a regimen of oral PPS significantly improved results [174].

- *Botulinum toxin* (grade of recommendation A, level of evidence 1) inhibits the release of calcitonin gene-related peptide and substance P from afferent nerves, and weakens pain [175, 176]. Several studies of intravesical Botox into the bladder wall indicated symptom relief in IC patients, without significant adverse events. In a pilot study of repeated injections where a total of 13 patients were followed up for 2 years, 10 patients reported a subjective improvement. Mean VAS scores, mean daytime and nighttime urinary frequency decreased significantly. At 1 and 2 years follow-up, the beneficial effects persisted in all patients [177]. These results are in contrast with those in another study from Kuo et al. [178] of Botox-A in ten patients with BPS. None of the patients became symptom-free; two showed only limited improvement in bladder capacity and pain score. Trigonal-only injection seems effective and long-lasting since 87% of patients reported improvement after a 3-month follow-up period in a study by Pinto et al. [179]. Further studies will be needed to obtain conclusive evidence for its efficacy, duration of effect, and side effect.

Intravesical Bacillus Calmette–Guérin (BCG) (not recommended) was initially reported to have some benefit in BPS/IC [180]; however, a subsequent randomized placebo-controlled trial of BPS/IC patients, who met the NIDDK research criteria, showed that there was no statistical difference at 34 weeks [181] (Table 5.6).

Table 5.6 Intravesical medications for treatment of BPS/IC

Intravesical therapy	RCT	GoE/LR
Heparin	No	C: 3
DMSO	Yes	B: 2
Hyaluronic acid	Yes	D: 1
Chondroitin sulfate	No	D: 4
Hyaluronic + chondroitin	Yes	C: 2
PPS	Yes	D: 4
BTX (intramural)	Yes	A: 1
		-A: 1 *ineffective*

GoE Grade of Evidence, *LR* Level Recommendation

5.12.1 Third to Fourth Line: Procedural Intervention

BPS/IC is a chronic and debilitating disease with an impairment of quality of life due to disabling symptoms. Surgical options should be considered only when all conservative treatments have failed.

Laser resection, augmentation cystoplasty, cystolysis, cystectomy, and urinary diversion may be the ultimate option for refractory BPS/IC patients [134]. Continent diversion may have better cosmetic and lifestyle outcome, but recurrence is a real possibility.

Posterior tibial nerve stimulation somewhat improved less than half of patients [181].

Sacral nerve neuromodulation as a treatment for BPS/IC in initial studies seems to relieve the symptoms of IC. Further studies are needed [182].

5.13 Conclusions

BPS/IC is a chronic, multifactorial disorder with symptoms of urinary frequency, urgency, and pelvic pain, often associated with other painful diseases, which profoundly affects patients' quality of life due to its disabling aspects. Pelvic pain in BPS/IC is a visceral pain syndrome with multiple pain generators, which can make the diagnosis difficult. Patients with a history of recurrent UTIs that are culture negative, those with endometriosis and significant bladder symptoms, with overactive bladder syndrome who have responded poorly to therapy, or with vulvodynia or chronic pelvic pain are all likely to have untreated BPS/IC. The primary providers of care for women with pelvic pain must consider the bladder as a very important source of pain. The earlier the diagnosis is made and therapy begun, the sooner patients with BPS/IC will experience improvement of their symptoms.

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6 Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC): A New Standardized Evaluation System

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The most accepted definition of bladder pain syndrome (BPS) was given by the International Society for the Study of Interstitial Cystitis (ESSIC): chronic pelvic pain, pressure or discomfort of greater than 6 months duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent desire to void or urinary frequency [1]. The diagnosis is often achieved after exclusion of confusable diseases as the cause of the symptoms. There is no clinical evidence about the possible relationship between duration of symptoms and possible early spontaneous resolution of symptoms. While ESSIC definition uses a 6 months duration of symptoms, the American Urological Association Guideline indicates that 6 weeks is enough [2]. The 6th International Consultation on Incontinence does not give a specific recommendation and states that it is up to the discretion of the physician and patient as to the proper interval between symptom onset and evaluation and diagnosis of a chronic condition [3].

The scientific committee of the International Consultation on Incontinence indicated the term "bladder pain syndrome" for the disorder that has been commonly referred to as interstitial cystitis (IC), avoiding the term painful bladder syndrome. The term IC is used to indicate an inflammation involving the bladder walls.

The term bladder pain syndrome is in accordance with the taxonomy of the International Association for the Study of Pain (IASP) and focuses well on the actual symptom complex. Bladder pain syndrome, as previously stated, indicates the presence of persistent or recurrent pain perceived in the sovrapubic region, accompanied by at least one other symptom, such as pain worsening with bladder filling and daytime and/or nighttime urinary frequency. The diagnosis implies the absence of proven infection or other obvious local pathology. Bladder pain syndrome is often associated with negative cognitive, behavioral, sexual, or emotional

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consequences. The Consultation suggests that the presence of the characteristic Hunner lesions should be considered a distinct disease, with a clinical different response to local treatment; moreover there is lack of evidence that non-Hunner bladder may develop Hunner lesions. The Consultation suggests to consider the Hunner lesions in symptomatic patients as "interstitial cystitis," thus indicating a true interstitial inflammation. To date, Hunner lesions may be considered as a distinct phenotype, but in the future, they may be classified as a separate disorder entirely, even though local symptoms may make it difficult to differentiate from bladder pain syndrome in the absence of endoscopy [3].

The diagnosis of BPS/IC is substantially clinical, according to the ESSIC definition [1]. After clinical suspicion, it is mandatory to exclude confusable diseases and identify phenotypical aspects of the disease. There are different severity grades, involved organs, possible allergies, and impact on quality of life. Some of these aspects can vary in the natural history of disease as well as after treatment. Patients affected by this disease have often stories that lasted for many years, carried out numerous tests and treatments. It is not always so easy to extrapolate the most important data from such complex stories. For male patients in whom bladder pain syndrome is mainly represented by chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) it is already available a clinical phenotyping system called UPOINTs, proposed by Shoskes for the tailored management of the pathology [4]. The system profiles patients in six qualitative clinical domains involved in the syndrome and indicates individual treatment targets. UPOINTs is an acronym standing for: Urinary, Psychosocial, Organ specific, Infection, Neurologic/Systemic, Tenderness and Sexual Dysfunction [5]. Traditional approach to manage CP/CPPS (i.e., monotherapy with alpha-blockers, antimuscarinics, phosphodiesterase type 5 inhibitors, and antibiotics) while working for some patents has failed in many patients diagnosed with this condition. Since no single management pathway is suitable for all patients, they should be managed according to their individual symptom pattern. This has led to the phenotypic multimodal approach using UPOINTs system. Although the validation of this approach is continuing, several studies confirmed the validity and applicability of the UPOINTs algorithm for the patient-tailored diagnosis and therapy of CP/CPPS [6]. Even if this approach has been extrapolated for IC/BPS by Nickel et al. [7], up-to-date there is no evidence about the validation of the UPOINTs method on BPS/IC.

To facilitate a diagnostic pathway and follow-up, we propose a standardized system dedicated to BPS/IC.

We elaborated a chart with 12 items, each considering a peculiar aspect/domain of the disease: voiding diary, Visual Analogue Scale (VAS), presence of pelvic/systemic pain, prevalence symptom (pain/LUTS), validated questionnaires, associated pathologies, allergies and intolerances, ESSIC classification, bladder anatomical capacity, and pelvic floor involvement (Fig. 6.1).

The first item (Fig. 6.1a) of the chart contains information from 3-days voiding diaries, including daytime frequency, nighttime frequency, and functional capacity. By definition such urinary symptoms are always present in these patients and improvement of these symptoms is a goal of the treatment [1]. The voiding diary

a.	**b.**	**c.**
MICTURITION DIARY Day-time frequency: Night-time frequency: Functional capacity:	**VAS** **Pelvic pain:** **Systemic pain:**	**Pain > LUTS** **Pain < LUTS** **Pain = LUTS**
d.	**e.**	**f.**
PUF Symptom: Disorder: Total:	**O'Leary-Saint IC** Symptom Index (ICSI) Problem Index (ICPI)	**QoL:** **PGI-I:**
g.	**h.**	**i.**
Associated pathologies:	**Autoimmune pathologies:**	**Allergies:** **Intolerances:**
j.	**k.**	**l.**
ESSIC Classification Cistosopy: Biopsy:	Anatomic bladder capacity:	Pelvic floor: (myo-fascial component) + ++ +++

Fig. 6.1 New proposal of standardized evaluation system for BPS/IC (A. Giammò)

highlights the urinary symptom that may have varying severity over time; sometimes a certain treatment acts more on urinary symptoms than on pain.

The second item (Fig. 6.1b) is represented by pain that represents the cardinal symptom of the pathology. We propose the use of the Visual Analogue Scale (VAS) to evaluate pain. The VAS allows to measure it and monitor changes during treatment.

The third box (Fig. 6.1c) analyzes the prevalence of pain with respect to lower urinary tract symptoms (LUTS). Sometimes the pain is exclusively pelvic and, in some cases, it involves other districts. Pain and LUTS can be variously represented in different cases. Sometimes pain symptoms prevail over LUTS, sometimes LUTS are the prevailing symptoms. Knowing this prevalence contributes in deciding proper treatment. Often, after treatment, this relationship changes. For example, pain may be reduced, but LUTS may remain: in this case LUTS treatment becomes a new goal.

The second line (Fig. 6.1d,e,f) is dedicated to the different validated questionnaires for the pathology. They are important to quantify the impact on quality of life and to numerically express the results of therapy. We included the most relevant questionnaires: Pelvic Pain Urgency Frequency questionnaire (PUF) [8], O'Leary Saint Interstitial Cystitis (Symptom Index and Problem index) [9], Quality of Life questionnaire (QoL), Personal Global Impression of Improvement (PGI-I).

Table 6.1 Possible comorbidities of BPS/IC

• Systemic erythematous lupus
• Sjogren syndrome
• Fibromyalgia
• Crohn disease
• Inflammatory bowel disease
• Chronic fatigue syndrome
• Thyroiditis
• Vulvodynia
• Migraine
• Rheumatoid arthritis
• Endometriosis
• Chronic prostatitis
• Pelvic floor dysfunction

The third line (Fig. 6.1g,h,i) allows to investigate all the comorbidities (Table 6.1), the possible allergies and intolerances, often present in these patients. These data are important to put the suspicion on comorbidity in order to request the intervention of the right specialists for a specific case. This is useful to obtain a multidisciplinary management of the disease. For example, due to the diet-sensitive nature of BCS/IC, the finding of alimentary problems can recommend the intervention of a nutritionist specialist.

The first record of the last line (Fig. 6.1j) is dedicated to the ESSIC classification [1], i.e., to endoscopic and histological phenotyping (Table 6.2). Even if its role is controversial, it is the only phenotyping tool available to date. In this way, the grid allows to relate the phenotype to the different clinical aspects recorded in the previous items. The aim of this item may allow to address a tailored treatment on the basis of the endoscopic and histological phenotype.

The second record of the last line (Fig. 6.1k) evaluates bladder capacity under anesthesia. This data is obtained from cystoscopy with hydrodistention at 80cmH2O filling pressure, which is considered important in the evaluation of disease. In this regard, it is important to identify patients with a significant reduction in anatomical bladder capacity that typically respond purely to standard treatments. In some cases, a significant reduction is an indication to perform a bladder augmentation surgery.

The last record (Fig. 6.1l) is dedicated to the involvement of pelvic floor. Many patients exhibit hypertonia and vaginal trigger points with varying grades of severity. These data can be useful to start a correct pelvic floor rehabilitation. In the event of significant anomalies noticed in this area, it will be advisable to request the intervention of a physiatrist.

The grid was created to be a simple and rapid tool to characterize the clinical picture and follow variations over time. Following each item of the chart, it is easy to collect all necessary information about the disease and have a global view of the clinical condition. The use of the grid during follow-up made it very easy to highlight changes in any item.

Another interesting aspect is the possibility to identify a relationship between ESSIC phenotype, clinical manifestations, and response to different therapies. For

Table 6.2 ESSIC classification of BPS/IC

Cystoscopy with hydrodistention					
		Not done	Normal	Glomerulations	Hunner lesion
Biopsy	Not done	XX	IX	2X	3X
	Normal	XA	1A	2A	3A
	Inconclusive	XB	IB	2B	3B
	Positive	XC	1C	2C	3C

example, it may be useful to understand why some patients respond to bladder instillations and others to oral therapy alone, or the impact of rehabilitative treatment.

By this grid we suggest a standardized method to the clinical approach, collecting useful information for clinical classification and management of the disease. In our opinion, the grid could represent a methodological guidance in the approach to the pathology.

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Prostate and Pain

7

Giulio Del Popolo, Gianmartin Cito, and Luca Gemma

7.1 Introduction

Chronic pelvic pain is generally described by chronic pain in the region of the pelvis. It is a common symptom of several structural and functional disorders affecting the anorectal area, urinary bladder, reproductive system, and pelvic floor musculature and its innervation. In contrast to structural diseases such as endometriosis in females, the pelvic pain is usually a functional complaint that cannot be explained by an organic pathology. Functional disorders are classified into anorectal (e.g., proctalgia fugax, levator ani syndrome, and unspecified anorectal pain), bladder [e.g., interstitial cystitis (IC)/bladder pain syndrome], and prostate syndromes [e.g., chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)]. IC/bladder pain syndrome is primarily diagnosed in women, whereas CP/CPPS is a diagnosis exclusive to men. Although IC and CP/CPPS have been largely considered different, they share many clinical features and are currently classified under the umbrella term, *urologic chronic pelvic pain syndromes* [1].

Prostatitis-related conditions represent the most common urologic diagnosis among men <50 years of age presenting to outpatient urology clinics [2]. Up to 10% of the male population will exhibit symptoms of this chronic syndrome at some point throughout their lifetime [3]. Any discussion of prostatitis as a disease requires attention to the definition of the illness, as "prostatitis" refers to a spectrum of syndromes characterized in varying degrees by bacterial infection of the prostate, genitourinary/pelvic pain (which may or may not include the prostate) and variable lower urinary tract symptoms (LUTS). Drawing on data collected from the

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Table 7.1 The National Institutes of Health (NIH) classification and definition of the categories of prostatitis

Category	Characteristic clinical features	Bacteriuria	Inflammation
I. Acute bacterial	Acute UTI	+	+
II. Chronic bacterial	Recurrent UTI caused by the same organism	NR	+
III. CP/CPPS	Primarily pain complains: Also voiding complaints and sexual dysfunction	–	NR
Type A: Inflammatory subtype (formerly: Nonbacterial prostatitis)		–	+
Type B: Noninflammatory subtype (formerly: Prostatodynia)		–	–
IV. Asymptomatic	Diagnosed during evaluation of other genitourinary complaints	–	+

Meares–Stamey four-glass test, which was pioneered a decade earlier, Drach and colleagues originally described their four categories of prostatitis in 1978: acute and chronic bacterial prostatitis, nonbacterial prostatitis, and prostatodynia. This classification system was further enhanced upon by the current NIH classification [4]. Within it, the authors kept the Category I and II definitions as acute and chronic bacterial prostatitis, respectively, while Category III, a nonbacterial version of prostatitis, characterized by genitourinary pain and LUTS in the absence of identifiable bacterial infection, was further described as either IIIA or inflammatory, versus IIIB or noninflammatory (previously prostatodynia). Finally, Category IV recognizes a common condition where asymptomatic patients exhibit evidence of prostatic inflammation (see Table 7.1).

Category III chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common form of the symptomatic prostatitis subtypes, comprising up to 90–95% of prostatitis diagnoses. It is defined as urologic pain or discomfort in the pelvic region, associated with urinary symptoms and/or sexual dysfunction, lasting for at least three of the previous 6 months. Differential diagnoses of pelvic pain such as urinary tract infection, cancer, anatomic abnormalities, or neurologic disorders need to be excluded. The distinction between IIIA and IIIB was based on the presence or absence of leukocytes in expressed prostatic secretions, post-prostatic massage urine, or semen specimens.

7.2 Pathophysiology

The etiology of CP/CPPS still remains unknown although different mechanisms may play an important role drawing similar, but not always the same, clinical phenotypes resultant. Several theories have been suggested to explain CP/CPPS pathogenesis including defective urothelial integrity and function, cryptic infections,

autoimmunity, endocrine imbalances, pelvic floor muscle spasm or tenderness, voiding dysfunction, peripheral and central sensitization and neuroplasticity, and psychosocial conditions [5].

Infection has been historically assumed to be the cause of CP/CPPS. It has been empirically treated with antibiotics although with limited success. In this regard, several studies have systematically failed to identify infectious agents as causative agents of this pathology [6]. Although the presence of an active infection in patients was not evident in almost all studies carried out up to date, CP/CPPS patients were found to have a significantly greater history of urethritis compared with age-matched controls [7]. While a primary infectious agent may not be the cause of the ongoing symptoms, infection may be the precipitating factor. In this regard, different microorganisms have been implicated such as *Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum, Trichomonas vaginalis, Candida* spp., and *Herpes Simplex* virus. In susceptible men, infectious urethritis or prostatitis could serve as the initial stimulus for chronic inflammation, although chronic inflammation and pain may persist after the infection has been cleared, possibly by an autoimmune and/or neurogenic mechanism. If this is the case, infection would be the triggering factor rather than the cause. In fact, using an animal model of prostatitis, the uropathogenic CP1 strain of *Escherichia coli*, isolated from a patient with CP/CPPS, has been shown to induce and sustain chronic pelvic pain that persisted long after bacterial clearance from the mouse genitourinary tract. This indicates a *genetic susceptibility* to chronic inflammation and pain but not to the infection itself [8]. Consequently, patients may develop inflammation and/or neuronal damage confined to the prostatic or pelvic area, which may be further augmented by the localized chronic inflammatory milieu. The unresolved chronic inflammation may potentiate tissue injury leading to pelvic floor dysfunction and central sensitization resulting in chronic pelvic pain.

Pelvic floor dysfunction as increased pelvic floor muscle spasm or tenderness has been also proposed as responsible for CP/CPPS symptoms. In fact, spasms or tight knots or trigger points in the pelvic floor muscles lateral and anterior to the prostate have been shown in CP/CPPS patients. It is recommended that practitioners should perform careful palpation of these muscles during the rectal exam in order to reproduce the patient's primary pain and to distinguish pain due to spasm from pain consequence from inflammation or other conditions. Besides, assessment of chronic pelvic pain tenderness by ultrasonography has linked pelvic floor muscle spasm to CP/CPPS [9]. However, whether pelvic floor muscle spasm is the causative agent or direct mediator of CP/CPPS symptoms still remains to be established. Usually patients with overactive pelvic floor can refer pelvic floor dysfunctions such as urinary reduced stream, frequency and increased post micturition residual urine and/or constipation and/or sexual disorder and/or bladder, perineum pain sometimes also groin and legs.

Chronic inflammation and autoimmunity has been deeply explored as the cause of CP/CPPS during the past two decades. Cumulative evidence points to the possibility that this syndrome is a consequence of dysregulated inflammation in the form of autoimmunity directed against prostate antigens (PAg). Indeed, an

autoimmune basis for CP/CPPS is a very prominent theory based on substantial evidence from studies in patients and animal models. One of the main and currently unanswered questions in CP/CPPS is how chronic pelvic pain develops and whether a mechanistic link with inflammation exists. Chronic pain is commonly triggered by chronic peripheral inflammation and nerve injury. This results in the release of neurotransmitters, lipid mediators, fragments of the complement system, neuropathic factors, cytokines, and chemokines in both the central and peripheral nervous system [10]. Both inflammatory and neuropathic pain can cause peripheral and central sensitization that can lead to allodynia, hyperalgesia, and spontaneous pain. Several authors specialized in this area suggest that inflammatory/neuropathic pain may play a central role in CP/CPPS [11]. Chronic pelvic pain include a combination of spontaneous visceral and referred somatic pain characteristics (i.e., pelvic visceral and referred perineal pain), and also the involvement of central nervous system (spinal cord and brain) in the sensitization's process [12]. The chronic presence of pelvic pain leaves specific brain neural imprints that persist for years. Alternatively, some of these neural abnormalities may be predisposing factors for CP/CPPS. However, it is unclear if these central changes are the cause or consequences of disease progression. Over thalamus and cerebral cortex, dorsal horn of the spinal cord may be involved in pelvic pain in CP/CPP. Central sensitization is caused by chemical and anatomical changes leading to hyperexcitability in the dorsal horn cells from persistent afferent C fiber bombardment by painful stimuli [11]. Chronic pain is induced and maintained by mediators released by immune cells (macrophages, lymphocytes, and mast cells), neurons, and glial cells that trigger peripheral and central sensitization. It has been proposed that neurogenic processes, autoimmune injury, and mast cells may contribute to inflammation and trigger pain development in CP/CPPS in males. Inflammatory stimuli are known to induce substance P (SP), calcitonin gene-related peptide, and nerve growth factor (NGF) secretion from nerve terminals, resulting in plasma extravasation, edema, and hyperalgesia, commonly referred to as neurogenic inflammation [13]. In this regard, mast cells have been suggested to play a central role. They are currently suggested as the main mediator and effector cells in disease progression from initiation to breaking of tolerance, neuronal activation, and, eventually, sensitization. Mast cells are tissue-resident immune cells that promote the infiltration of inflammatory cells such as macrophages and lymphocytes into tissues, which when activated secrete cytokines that further activate mucosal mast cells, perpetuating the cycle of inflammation. Moreover, mast cells respond to SP and NGF secreted by neuronal terminals degranulating and releasing histamine, serotonin, cytokines, chemokines, prostaglandins, and neuropeptides such as brain-derived neurotrophic factor, neurotrophin-3, and more NGF and SP. The inflammation induced by mast cell activation and degranulation might result in irreversibly altered neurotransmission and thus explain, at least partly, the chronic nature of pain in CP/CPPS. It has been shown that CP/CPPS patients have elevated levels of mast cell attractant chemokines CCL2 (MCP-1) and CCL3 (MIP-1α) in prostate secretions, which associated with clinical pain. These results suggest that NGF and mast cells secretion products are potential mediators involved in pain sensitization mechanisms in CP/ CPPS. In agreement,

treatment with pentosan polysulfate, a stabilizer of mast cells, was shown to ameliorate symptoms in CP/CPPS patients [14]. Although NGF seems to sensitize sympathetic neurons to proinflammatory stimuli [15], tanezumab, a monoclonal antibody against NGF, showed no significant improvement compared with placebo suggesting that anti-NGF therapy is not sufficient by itself to reduce symptoms [16]. Cytokines secreted by mast cells have been shown to control Th17/Treg cell differentiation and plasticity [17]. In this regard, Murphy et al. recently provided some controversial evidence indicating that IL-17 would be crucial for the induction but not maintenance of pelvic pain in experimental autoimmune prostatitis (EAP) [18]. Authors showed that prophylactic treatment with IL-17-blocking antibodies was sufficient to abolish pelvic pain development. However, they surprisingly did not show any data about prostate tissue inflammation or cell infiltration in order to definitively assess if pelvic pain was related to prostate inflammation. Besides, the authors remarkably showed that they failed in preventing or ameliorating chronic pelvic pain when administering a therapeutic treatment of IL-17-blocking antibodies on day 10 post EAP induction. However, it remains to be established if removal of inflammation can reverse or ameliorate mast cell infiltration, neuronal sensitization, and chronic pelvic pain. Additional studies are needed to establish the relationship between prostatitis induction, prostate mast cell activation/degranulation, and the precise mechanisms by which they would induce chronic pelvic pain (see Fig. 7.1).

Considering the potential role of autoimmunity and chronic inflammation to sustain, recent studies have evaluated a link with non-urological chronic overlapping pain conditions (COPCs); in particular fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome share many demographic, clinical, and psychosocial

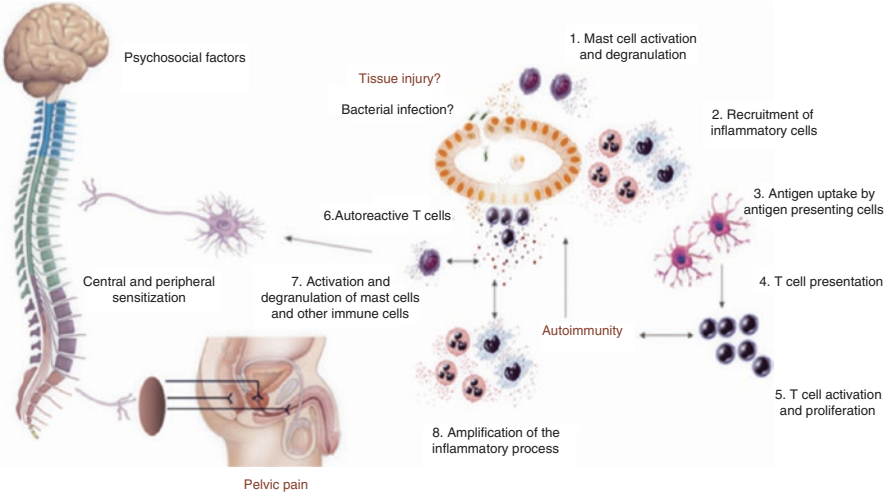

Fig. 7.1 Proposed model of the pathophysiological mechanisms involved in prostate inflammation and chronic pelvic pain development in chronic prostatitis/chronic pelvic pain syndrome [1]

features, as well as pain-related subjective and objective features, possibly reflecting common underlying mechanisms and/or pathophysiology [19].

7.3 Clinical Management

7.3.1 Diagnosis

CP/CPPS could be featured by different symptoms, lasting and fluctuating over the time. Pain, urinary, sexual dysfunction, and psychosocial symptoms are referred by the patients [20]. *Pain symptoms* include pain or discomfort in one or more urogenital regions between perineum, rectum, supra-pube, testicles, penis, lower back, abdomen, inguinal region, groin, pain on urination or ejaculaction, muscle tenderness in abdominal, pelvic region. *Urinary symptoms* regard voiding (weak stream, straining and hesitancy), storage (urgency, urge incontinence, increased urinary frequency, nocturia and dysuria) LUTS, or recurrent urinary tract infections (UTI). *Sexual alterations* include erectile and/or ejaculatory dysfunction (premature, delayed or pain during, or after, ejaculation), decreased libido. Finally, *psychosocial symptoms* such as anxiety, stress, depression, cognitive and behavioral impairment might be considered. Patients can be considered to be in the early stages of the disease if they have experienced persistent, recurrent symptoms for <6 months and are antibiotic-naive, or in the later stages of the disease if they have experienced persistent, recurrent symptoms for >6 months and are refractory to initial lines of pharmacotherapy.

As in any clinical encounter, a thorough history is an important step in establishing a diagnosis and developing a differential diagnosis of other confusable diseases that must be ruled out in those presenting with symptoms of CP/CPPS [21]. Validated symptom-scoring instruments for CBP and CP/ CPPS include: the NIH Chronic Prostatitis Symptom Index (NIH-CPSI; evaluating pain, voiding and impact on QoL); the International Prostate Symptom Score (IPSS; urinary symptoms and impact on QoL); and the more recent Urinary, Psychosocial, Organ-specific, Infection, Neurological/systemic, and Tenderness (UPOINT) classification, which aims to stratify patients into specific symptom-led phenotypes [22]. It classified patients' symptoms into six distinct subgroups: urinary, psychosocial, organ-specific, infectious, neurologic, and tenderness (pelvic floor tenderness). Patients could be classified into one or, in most cases, multiple domains. The five-item version of the International Index of Erectile Function (IIEF-5) or Sexual Health Inventory for Men (SHIM) specifically evaluate ED. Patients should be screened for psychosocial symptoms (e.g., anxiety or stress) using either the psychosocial yellow flag system and/or Patient Health Questionnaire-9 (PHQ-9) and/or Generalised Anxiety Disorder-7 (GAD-7) scales. If a clinically relevant level of psychosocial symptoms is observed, referral to a psychosocial specialist (e.g., psychiatrist, specialist psychologist, or cognitive behavioral therapist) should be considered.

A focused *physical examination*, including a pelvic exam and digital rectal exam (DRE), is considered mandatory in the evaluation of any patient with symptoms of

CP/CPPS. *Urine dipstick* and/or midstream urine for culture/microscopy are useful to confirm the presence of UTI and/or hematuria. PSA test could be used in the case of suspected prostatic cancer, with a DRE suspicious and age patient >50 years. The classic four-glass test developed by Meares and Stamey could represent the gold standard to evaluate whether there is a bacterial cause; the purpose is localization of bacteria and inflammation to the urethra, prostate, or bladder. The first specimen—voided bladder 1 (VB1)—is the initial 10 cc of urine from a collection and corresponds to the urethra. The second specimen—VB2 or midstream collection—corresponds to bladder urine. A follow-up prostate massage results in the expressed prostatic secretion (EPS) specimen. Finally, the VB3 or post-prostatic massage specimen is the first 10 cc of urine collected immediately following prostatic massage and represents an alternative prostate-specific specimen.

The role of *imaging* in the diagnosis of CP/CPPS remains a useful tool to rule out confusable diseases and should be used as indicated on a case-by-case basis. Except for specific indications, no imaging study is considered recommended or mandatory in various clinical practice guidelines in the evaluation of CP/CPPS. Although it remains a useful tool in evaluation of the prostate, ultrasound has little value in establishing diagnosis of CP/CPPS. It can be utilized to determine post-void residual bladder volumes, particularly in men with obstructive voiding symptoms. Confusable diseases such as obstructed seminal vesicles, prostatic abscess, and prostatic calculi may also be diagnosed using transrectal or transabdominal ultrasound of the prostate and should be considered when appropriate. Cystoscopy should be reserved for those patients presenting with microscopic or macroscopic hematuria, treatment refractory storage or voiding symptoms, abnormal urine cytology, or for those in whom malignancy is suspected.

7.3.2 Treatments

Multiple reviews and meta-analyses have been available in recent years regarding the treatment and management of CP/CPPS. Management of CP/CPPS involves a multimodal (pharmacological and non-pharmacological) tailored approach [23]. *Pharmacological* interventions include alpha blockers, 5-alpha reductase inhibitors, antibiotic therapy, anti-inflammatories, phytotherapy, botulinum toxin A (BTA), allopurinol, traditional medicine, other pharmacological agents, alone or in combination. Although with low-quality evidence, alpha blockers may reduce prostatitis symptoms based on a reduction in NIH-CPSI scores with an increased incidence of minor adverse events such as dizziness and hypotension; 5-alpha reductase inhibitors, antibiotics, anti-inflammatories, and phytotherapy may cause a small decrease in prostatitis symptoms and may not be associated with a greater incidence of adverse events. Intraprostatic BTA injection may cause an important reduction in prostatitis symptoms with procedure-related adverse events (hematuria), but pelvic floor muscle BTA injection may not have the same effects. Allopurinol may also be ineffective for the reduction of symptoms. The traditional Chinese medicine, with a low-quality evidence, showed they may reduce prostatitis symptoms without an

enlarged incidence in adverse events. While, anticholinergics, OM-89, pentosan, and pregabalin might be ineffective (moderate- to high-quality evidence). Low-quality evidence indicates that antidepressants and tanezumab may be ineffective for the reduction of clinical symptoms; at the same time, mepartricin and phosphodiesterase inhibitors may be beneficial, without an increased incidence in adverse events (low-quality evidence). Some *non-pharmacological* interventions such as acupuncture and extracorporeal shockwave therapy are likely to result in a decrease in prostatitis symptoms and may not be associated with a greater incidence of adverse event [24].

Using multiple interventions to target different symptom areas simultaneously may be expected to provide more benefits. Therefore, multimodal/combined treatment should be uniquely designed for each individual patient, according to history, physical examination, and clinical investigations.

7.4 Conclusion

Prostate and pelvic floor can be considered as a single functional entity. Prostate dysfunctions impact the pelvic floor activity and vice versa the overactive pelvic floor can lead to urological, sexual, and colo-proctological dysfunctions. Therefore, an early approach that should not only be pharmacological but also include lifestyle and reduction of perineal muscular activity can increase therapeutic success rate. New randomized trials are needed in order to have a real scientific evidence-based treatment.

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Vulva and Pain

8

Leonardo Micheletti, Gianluigi Radici, and Mario Preti

8.1 Introduction

This chapter addresses a special type of vulvar pain named *Vulvodynia* which represents a challenge to healthcare providers. The accurate diagnosis and adequate treatment of this complex syndrome requires understanding the recent neurobiological knowledge that classifies pain into three different forms: nociceptive, inflammatory, and pathological pain, with the latter subdivided into neuropathic and dysfunctional [1]. *Nociceptive pain* is protective, adaptive, high-threshold pain provoked by noxious stimuli. *Inflammatory pain* is protective, adaptive, low-threshold pain associated with peripheral tissue damage and inflammation. *Pathological pain* is non-protective, maladaptive, low-threshold pain, representing a disease state of the nervous system caused either by structural damage of the nervous system (*neuropathic pain*) or by its abnormal function (*dysfunctional pain*) [1].

Inflammatory, *neuropathic,* and *dysfunctional pain* share the phenomenon of *sensitization*, characterized by reduced threshold, amplified response, and spontaneous discharges in nociceptive neurons. Abnormal central sensitization can be interpreted as abnormal long-term potentiation, defined as a persistent increase in synaptic strength in central nociceptive pathways, induced by exposure to peripheral precipitating events, specifically peripheral tissue damage and inflammation, in the presence of an individual predisposition to abnormal pain persistence. As a consequence, allodynia, hyperalgesia, and spontaneous pain persist beyond peripheral tissue healing, becoming chronic and maladaptive [2].

Clinically, in ***inflammatory pain****, sensitization* produces pain hypersensitivity, spontaneous pain, allodynia defined as pain due to a stimulus that does not normally provoke pain, hyperalgesia defined as exaggerated and prolonged pain in response

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to stimulus that normally provokes pain, and secondary hyperalgesia which is spread of pain beyond the site of tissue damage [3, 4]. The inflammation-induced sensitization is reversible since it represents reversible physiological pain hypersensitivity in reaction to peripheral tissue inflammation.

Peripheral ***neuropathic pain*** most commonly results from neural lesions caused by mechanical trauma, metabolic diseases, neurotoxic chemicals, infection, or tumor invasion, while *central neuropathic pain* most commonly results from spinal cord injury, stroke, or multiple sclerosis. Many patients with structural damage of the somatosensory system have only negative symptoms, hypoesthesia and hypoalgesia, reflecting direct neuronal damage with compromised transduction or transmission of sensory information. Some patients also have positive symptoms, such as spontaneous pain, allodynia, hyperalgesia, paresthesia, and dysesthesia. A small percentage of patients have only positive symptoms without sensory deficits that can be explained by ectopic action potential discharges generated along the nociceptive pathways, peripheral sensitization of the uninjured nociceptors, central sensitization, and loss of pain inhibitory control systems [5].

Dysfunctional pain occurs in some painful syndromes, such as fibromyalgia, irritable bowel syndrome, interstitial cystitis (better defined as 'pain bladder syndrome since there is no inflammation), tension-type headache, and temporomandibular joint disease, in which there is pain hypersensitivity but no noxious stimulus, no inflammation, and no structural damage to the somatosensory nervous system [1]. These syndromes are characterized by a similar abnormal and widespread increase in pain sensitivity, which probably reflect a common contribution of central sensitization. This may account for the unexpectedly high comorbid rate of these apparently different painful syndromes [6].

In 2015, the International Society for the Study of Vulvovaginal Disease (ISSVD), the International Society for the Study of Women's Sexual Health (ISSWSH), and the International Pelvic Pain Society (IPPS) endorsed a shared terminology and classification which identified two types of vulvar pain: **persistent vulvar pain** and **vulvodynia** [7].

Pain is defined as persistent or chronic if it persists over a period of at least 3 months.

Persistent vulvar pain is caused by specific disorders such as infectious diseases (e.g., recurrent candidiasis, genital herpes), inflammatory diseases (e.g., lichen sclerosus, lichen planus, immunobullous disorders), neoplasms (e.g., Paget disease, squamous cell carcinoma), neurologic disorders (e.g., postherpetic neuralgia, nerve compression or trauma), trauma (e.g., obstetric lacerations, female genital cutting), iatrogenic disorders (e.g., postoperative, chemotherapy, radiation), and hormonal deficiencies (e.g., genitourinary syndrome of menopause, lactational amenorrhea).

All these vulvar disorders are not investigated since the aim of this chapter is to focus on vulvodynia.

8.2 Vulvodynia

The definition of vulvodynia is "vulvar pain of at least 3 months duration, without clear identifiable cause, which may have potential associated factors" [7]. Older terms such as vulvar vestibular syndrome, vestibulitis, or vulvar vestibulitis may not be longer in use.

Vulvodynia is categorized depending on location, provocation, onset, and temporal pattern.

- According to location, vulvodynia can be generalized or localized. Generalized means involvement of the whole vulva, and localized means involvement of a portion of the vulva, such as the vaginal vestibule (vestibulodynia), clitoris (clitorodynia), or one side of the vulva (hemivulvodynia). Depending on provocation, vulvodynia is subdivided into provoked, spontaneous, or mixed (provoked and spontaneous). Provoked refers to pain elicited by physical contact. Such contact may be sexual, nonsexual or both, i.e., vaginal penetration, clothing, pressure tampon insertion, cotton-tipped applicator pressure, and fingertip pressure. Spontaneous refers to pain that occurs without any provoking physical contact.
- Concerning onset, provoked vulvodynia is referred to as primary or secondary depending on whether the onset of the pain occurred with first provoking physical contact or not.
- Finally, according to the temporal pattern, vulvodynia can be constant or intermittent, depending on whether the pain is always present or not.

Provoked vestibulodynia (PVD), pain localized to the vaginal entrance or vestibule, is considered the most prevalent subtype of vulvodynia [8].

8.2.1 Pathophysiology

PVD in earlier literature has been described as neuropathic or inflammatory pain, but this description is confusing based on contemporary neurobiological classification of pain, as it implies a neural or inflammatory lesion.

From a neurobiological perspective, PVD is a **dysfunctional vulvar pain** caused by abnormal function of the nervous system itself, not related to a specific vulvar disorder responsible for inflammatory pain, or a neural lesion responsible for neuropathic pain [9].

No single causative factor for PVD, or chronic pain in general, has been identified, and pathophysiology is likely multifactorial and complex, and differs from person to person [10].

It has been proposed that multiple genetic factors in concert with environmental exposures (such as infection, trauma, and psychological stress) enhance pain sensitization and/or psychological distress to increase susceptibility to chronic pain [11].

8.2.2 Symptoms

Pain is most often described as burning, but sometimes in other qualitative terms, such as stinging, tearing, or pressure-like. Superficial dyspareunia is usually present in PVD. Pain is usually associated with many other symptoms, including physical disability with compromised sitting or walking, sexual dysfunction, and psychological distress.

Despite vulvodynia being recognized as one of the most common causes of sexual pain [12], it is not mentioned as a differential diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) [13]. A classification for sexual pain is provided in the DSM-5, namely "genito-pelvic pain/penetration disorder," listed as a sexual dysfunction. Using the DSM-5 terminology, vulvodynia could be classified as a psychiatric disorder and a sexual dysfunction. This has proved controversial [14] since to classify vulvar pain as a psychiatric disorder is neither helpful nor informative both for clinicians and for patients; actually the clinician could be driven to adopt a not contemporary evidence-based approach to management.

8.2.3 Diagnosis

The primary diagnostic goal is to determine whether the woman suffers from vulvodynia, as dysfunctional pain opposed to inflammatory or neuropathic pain: that can be done through a correct history and clinical examination.

8.2.3.1 History

A detailed history is essential to vulvar pain assessment. It has to include family and personal history of comorbid chronic painful diseases, relevant psychological states (anxiety, depression, catastrophizing, hypervigilance, fear of pain, post-traumatic stress disorder), childhood emotional trauma (abuse, assault, neglect), sexuality (desire, arousal, orgasm, frequency and satisfaction with sex, sexual repertoire, and sexual distress), pain characteristics (location, elicitors, quality, intensity, onset, and temporal pattern), history of physical trauma, and surgery.

Concurrent painful diseases must be investigated since almost half of women with vulvodynia report one or more other chronic pain conditions [15] that have been termed chronic overlapping pain conditions (COPCs) [16], which include vulvodynia, temporomandibular disorders, myalgic encephalomyelitis/chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, fibromyalgia, endometriosis, chronic tension-type and migraine headache and chronic low back pain. Enhanced pain sensitivity distant to the primary pain site is a common feature in patients with chronic pain [4], and this has been demonstrated in PVD [17].

Psychological states and distress influence pain sensitivity, increasing the risk for transition of acute to chronic pain [18]. Anxiety and depression are highly associated with chronic pain, and subjects suffering from these disorders are at high risk

to develop chronic pain conditions [19]. Anxiety is 10 times more common and depression three times more common in women with PVD compared with controls [20]. Risk factors for chronic pain and PVD are also adverse childhood experiences including abuse, living in fear of abuse, and social trauma such as bullying, exclusion, or lack of support [21].

Post-traumatic stress disorder (PTSD), a form of severe anxiety, is known to be associated with increased pain levels and pain disability [22], and women suffering from PTSD has two to three times higher risk for PVD development [20].

8.2.3.2 Clinical Examination

The diagnosis of vulvodynia is established after excluding the inflammatory and neuropathic nature of vulvar pain.

A clinician has to examine the vulva with the naked eye or with a 2- or 3-power magnifying lens. A higher power magnification with a colposcope is not recommended. Acetic acid, Lugol's iodine solution, and toluidine blue are useless and misleading.

Speculum examination is mandatory to identify relevant vaginal findings, such as atrophy, erythema, erosions, ulcerations, abnormal discharge, or synechiae. In the presence of vaginal discharge, a specimen has to be collected for microbiology investigations. Testing for human papillomavirus is useless.

The cotton swab test (Q-tip test) aims to identify vulvar areas of mechanical allodynia, i.e., provoked pain. Testing can be performed in either a clockwise direction or according to anatomical structures, including the medial tights, mons pubis, labia majora, labia minora, interlabial sulcus, clitoral hood, perineum, and vestibule. The vestibule is tested at the 2:00, 4:00, 6:00, 8:00, and 10:00 positions. The patient is asked to quantify the provoked pain on a visual analog scale, a numerical rating scale, or verbal categorical rating scale.

QST (e.g., von Frey filaments, gesiometer, and current perception threshold sensory testing device) is not recommended in clinical practice.

Hypertonic pelvic floor muscle dysfunction can be identified by intravaginal muscle palpation with a single digit, lubricated with anesthetic jelly. Applying a posterior pressure allows the clinician to determine the tone of the pubovaginal portion of the levator ani. Findings indicative of pelvic floor hypertonicity include tightening around the examiner's finger, lifting of the posterior vaginal wall, and drawing in of the perineum. Often patients have so much muscle tension at rest that they are unable to produce further contraction. Moreover, many patients cannot relax completely or quickly, or demonstrate rebound tightening after relaxation.

8.2.4 Management

The goals of treatment are pain relief and improvement in the quality of life and sexual function.

Many treatments for vulvodynia are widely described in the literature, and some guidelines are available [23, 24]. However, studies that inform the guidelines are not

of high quality because they have many limitations including poor patient selection, inadequate drug prescription, low statistical power, lack of standard treatment outcome measures, limited follow-up data, lack of randomization, or randomization with methodological bias. Despite these limitations, most women do improve with treatment, and many become pain-free [25].

No single treatment is effective for all women [24], but there is good evidence that multidisciplinary management is effective [26].

Because PVD is a multifactorial syndrome, it requires an individually tailored and multidisciplinary approach with a combination of therapies that include counseling, psychological therapy, medical treatment, and physiotherapy [27–29]. Surgery can be proposed only as a last resort, emerging modalities, including hypnotherapy and acupuncture, require further validation.

Here, we will focus on what has been proven to be the most useful treatment approach in our daily clinical practice.

8.2.4.1 Counseling

Interdisciplinary skill specifically in neurobiological, algological, and psychological field is of the utmost importance for a successful counseling.

Counseling key points are empathy and education.

Empathy and reassurance are effective therapeutic tools. Empathy has been shown to activate the same brain regions as activated in chronic pain and placebo [30], in addition placebo effect is enhanced when the clinician adopts an emotionally warm, empathic reassuring style and fully informed on the nature of placebo [31, 32].

On the contrary, clinician uncertainty regarding diagnosis and management can potentially induce nocebo (the opposite of placebo) hyperalgesia [33]. In effect, the clinician, through his communication style, can become a therapeutic agent to the patient in connection with providing effective treatment interventions [31].

Education, generally speaking, has been shown to reduce pain intensity, disability, anxiety, and stress [25, 34]; it reduces also sexual and psychological distress [35]. A clinician has to explain with simple words what is PVD and that pain can occur in the absence of peripheral diseases such as cancer, infection, or trauma.

To have a name for the pain, to know that PVD is a common condition and that with treatment most women can expect a significant improvement of symptoms, even if the improvement can be slow, not complete, and not definitive, may provide enormous relief and reduce pain-related anxiety, and pain itself. In addition, explaining treatment and its rationale can enhance the placebo effect, defined as a positive expectation of pain relief, that increases the therapeutic efficacy of treatment.

It is also useful encouraging the partner to be present since it is a helpful opportunity to educate both the woman and the partner about pain neurobiology and to provide a safe place for them to discuss the effect of pain on their sexual intimacy and relationship.

The final aim of education is to drive the woman to understand that her pain is due to a real, although complex, disease identified with a specific name (PVD) and to be informed that becoming self-manager of her pain can contribute increasing treatment efficacy.

Counseling includes also education regarding gentle vulvar care, to eliminate the possibility of contact dermatitis responsible for pain exacerbation. Vulvar irritants, such as perfumed products, wipes, unnecessary topical medications, soaps, and over-washing, should be avoided. The vulva can be cleaned with cool or warm water only. After washing, vegetable or olive oil can be used as an emollient to improve the skin moisture and barrier function. Tight and synthetic clothing should be avoided. Cotton underwear during the day and none at night are recommended. If menstrual pads are irritating, cotton pads can be useful. Cool gel packs can give relief. Adequate lubrication is required for sexual intercourse. Irritating activities such as cycling or horse riding should be avoided.

8.2.4.2 Psychological Therapies

Psychological interventions are effective and recommended [27, 36].

Both cognitive behavioral therapy and supportive psychotherapy are effective in reducing sexual pain and improving sexual function [36]. Psychotherapy that promotes acceptance of the pain and a reduced sense of injustice has been shown to improve sexual function [37, 38] together with mindfulness-based therapy [39].

A combined consultation with the partner is always helpful, especially when penetrative sex is too painful, so an exploration of intimacy that is not painful can be discussed with the couple [40].

8.2.4.3 Medical Treatment

The mainstay of medical treatment of vulvodynia is oral therapy with pain neuromodulators, which include tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and calcium channel α2-δ ligands anticonvulsants [27, 41, 42]. Women should be advised that all these drugs are prescribed as pain neuromodulators and not as antidepressants or anticonvulsants, that the benefit can take several weeks (sometimes up to 12 weeks) to appear, and side effects are more common on the beginning but wane with continued use.

Amitriptyline is the best studied and most commonly prescribed TCA. The efficacy of amitriptyline is superior to that of desipramine. The analgesic efficacy is mediated by strengthening of descending pain-inhibitory system through inhibition of serotonin and norepinephrine reuptake at inhibitory synapses, leading to increased concentration of the neurotransmitters in the synaptic cleft. TCAs also inhibit sodium channels at the periphery.

SNRIs include duloxetine and venlafaxine. Like amitriptyline, they act centrally by inhibiting neuronal reuptake of norepinephrine and serotonin, thereby enhancing the activity of the descending inhibitory pathways that modulate afferent nociceptive input.

Calcium channel α2-δ ligands include gabapentin and pregabalin. They block calcium channels on central terminals of primary nociceptive neurons, leading to a decreased release of glutamate at excitatory synapses, thereby reducing the transmission of the nociceptive signal from one neuron to another.

Both TACs and SNRIs can be combined with anticonvulsants, but TACs cannot be combined with SNRIs for the risk of serotonin syndrome. Oral pain

neuromodulators are prescribed in lower doses than would be used for depression or epilepsy. These drugs should be initiated at low doses; then a slow titration should be performed up to efficacy and side effects. Women should be aware that therapy is chronic. If symptoms completely resolve, the dose can be titrated to the lowest effective dose.

Along with oral therapy, lidocaine 2–5% gel or ointment is recommended by some authors [10, 43], while others do not recommend continued use due to lack of evidence [27].

Women should be aware that lidocaine may cause burning or sting for some minutes after the application. Treatment should be stopped if it provokes contact dermatitis. Male sexual partners can experience penile numbness and oral contact should be avoided. Benzocaine is not advised because of its major potential for sensitization.

8.2.4.4 Physiotherapy

Pelvic floor (PF) overactivity contributes to PVD, but considering the complexity of PVD and comorbid pain conditions, skilled physiotherapists are required in pelvic and general physiotherapy as well as chronic pain management.

The PF forms part of an integrated neuromuscular system with functions including mechanical support, mobility, reproduction, respiration, evacuation, as well as sexual function. So the physiotherapist must work in synergy with the other specialists, aware of related systems, central pain mechanisms and the role played by psychological distress or trauma. As a matter of fact, the physiotherapist, through regular contact, is in a privileged and valuable position to develop trust and rapport and may be often the first person to whom fear and abuse are revealed, in the same time, the work associated with physiotherapy may trigger memories of trauma.

Improved sexual function and reduced pain with intercourse with PF therapy is reported [44] especially when is part of a multidisciplinary approach [27]. The aim of PF physiotherapy is to reduce overactivity and desensitize the CNS [45], equally to increase awareness and proprioception, normalize tone, improve muscle discrimination, and reduce fear of penetration.

Adjunctive therapies include manual therapy techniques, biofeedback, dilators, transcutaneous electrical nerve stimulation (TENS), and gentle exercise programs such as walking, swimming, yoga, stretching, and massage.

In accordance with the woman, the partner can be involved in the treatment, knowing that this, on one hand, can medicalize their intimacy and, on the other hand, that the woman may fear an unintentional sexual arousal of the partner.

8.2.4.5 Surgery

Vestibulectomy, a surgical excision of all or part of the vaginal vestibule followed by covering of the resulting defect with vaginal mucosa, has been proposed in women suffering from PVD; however evidence is limited because of methodological issues including lack of placebo controls, different surgical procedures, different methods for evaluations of outcomes, and insufficient data on long-term outcome.

Some studies reviewing vulvodynia treatment has shown a complete pain relief in 70% of women with PVD following vestibulectomy; however, long-term follow-up has demonstrated that the response to vestibulectomy is comparable to conservative management [24, 46]. Moreover, surgery is an invasive intervention with possible complications including bleeding, hematoma, infection, inclusion cyst, Bartholin cyst, wound dehiscence, and scar tissue formation.

Finally, laser vaporization of the vulvar epithelium and other laser procedures are not supported by scientific evidence and lack biological plausibility; therefore they are not recommended.

8.3 Summary

1. PVD, as the most frequent subtype of vulvodynia, is a persistent and multifactorial vulvar pain syndrome.
2. From a neurobiological perspective, PVD is a dysfunctional vulvar pain caused by abnormal function of the nervous system itself, not related to a specific vulvar disorder responsible for inflammatory pain, or a neural lesion responsible for neuropathic pain.
3. The primary diagnostic goal is to determine whether the woman suffers from PVD, as dysfunctional pain opposed to inflammatory or neuropathic pain.
4. Because PVD is a multifactorial syndrome, it requires an individually tailored and multimodal therapeutic approach that includes counseling, psychological therapy, medical treatment, and physiotherapy.
5. Surgery can be proposed only as a last resort.

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Anus and Pain

9

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9.1 Introduction

Anal pain is a common, nonspecific but potentially highly debilitating symptom, with significant impairment in quality of life, psychological distress, and inability to work.

It affects between 6.6% and 11.6% of the population, though only about a third of patients consults a physician [1] and it is present in a wide range of different disturbances and pathologies.

It is frequently considered as an idiopathic problem but in some cases it could be due to nonfunctional or organic diseases, which can be identified in about 15% of patients [2].

A wide range of definitions and classification has been used in the literature during the years regarding the taxonomy of chronic anal and pelvic pain. For these reasons frequently this topic suffers a lack of clarity in terms of classification, diagnostic tools, and treatment options.

Moreover Rome IV criteria divide anorectal functional pains into Proctalgia fugax (which is typified by short-lasting episodes of severe pain), unspecified anorectal pain, and levator ani syndrome (in which the pain lasts for periods of more than 20 min at a time or is permanent) [3].

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9.2 Diagnosis of Nonfunctional Chronic Anal Pain

In case of a suspected nonfunctional chronic anal pain, a stepwise approach is essential to be sure that no possible diagnosis is missed and we have to approach the patients with a clear diagnostic algorithm in mind [4].

The first step is an accurate history data collection, including known previous anorectal diseases, complained problems, surgical procedure or other treatments carried out, and potential anal trauma.

Consecutive step is a detailed visual inspection and digital rectal exam. Many common anorectal diseases (thrombosed hemorrhoids, anal fissures, stricture or ulcerations, fungal or viral infections such as condyloma or herpes) can be identified with this simple step. In women, a bimanual exam can reveal a gynecologic pathology (endometriosis, vulvodynia, prolapse, or mesh erosion) which can also induce anal pain.

After inspection, anoscopy can confirm first visual diagnosis or rule out deep sepsis with endoanal sinus not fistulized to skin, anal/distal rectal cancer or rectal stricture. In absence of other pathologic signs at this moment a rigid proctoscopy can identify rectal proctitis or a solitary rectal ulcer.

An office transanal ultrasound examination or a MRI of the pelvis can reveal retrorectal pathology and cryptic perianal abscess. A MRI of the spine can exclude herniated disc and other neurologic syndromes [5, 6].

9.2.1 Most Common Nonfunctional Causes of Anal Pain

Common people usually associate anal pain to **hemorrhoids**. It is routinely false: internal anal canal is covered by insensitive mucosa, for this reason pain is not typically associated with internal hemorrhoids. Hemorrhoids rarely are painful unless they became complicated and develop ***thrombosis or necrosis***. Usually these events involve the distal part of anal canal and may cause significant pain because the anoderm is richly innervated by somatic nerves [7, 8].

Thrombosis of hemorrhoids is commonly due to an acute increase of blood pressure in hemorrhoidal dilated veins during physical efforts like work or hard defecation or during last part of pregnancy. In case of thrombosis of hemorrhoids the pain is temporary and stops quickly after surgical incision and even spontaneously in few days.

On the contrary, anal pain is very frequent after surgical removal of hemorrhoids. ***Hemorrhoidectomy*** is a procedure in which the severe pain (opioid requirements in analgesic management) occurs in 20–40% of patients [9]. Postoperative pain is the main reason for delayed patient discharge and delayed return to work after hemorrhoidectomy. Spasm of the internal anal sphincter is thought to be the source of pain and it may be an important component of postoperative pain [10]. In the last 20 years different procedures have been proposed to obtain less painful treatment of hemorrhoids. The use of staplers, devices for dearterialization, laser, or radiofrequency

delivery have demonstrated good results in terms of postoperative pain. A Cochrane review of ten studies demonstrated significantly lower pain scores (using a validated visual analog scale) on follow-up in patients receiving Ligasure vs. conventional hemorrhoidectomy [11].

Despite a Cochrane review showed no significant differences in complication rates (including postoperative pain) between stapled hemorrhoidopexy vs. conventional excisional hemorrhoidectomy [12] a more recent meta-analysis found that there was less pain after stapled hemorrhoidopexy, as evidenced by lower pain scores at rest and on defecation [13]. Histological studies on postoperative specimens of anal canal have shown that peripheral nerve trunks of rectal submucosa are distorted and surrounded by cicatricial fibrotic tissue similar to traumatic neuroma as a possible cause of chronic anal pain after stapled hemorrhoidopexy [14].

A systematic review and meta-analysis of randomized clinical trials showed that the mean VAS of early postoperative pain after Doppler-guided transanal hemorrhoidal dearterialization (THD) was significantly lower than excisional hemorrhoidectomy [15].

The most common cause of anal pain is doubtless **anal fissure**. Anal fissures are common; in one colorectal clinic's experience, the prevalence of fissures among its patients was 10%. Fissures occur much more frequently than many expect, and are often overlooked by practitioners [16].

This anal wound leads to an important and highly debilitating pain. It can last also for many years and could be continuous or for some hours after defecation. It is usually connected with an important anal resting and involuntary hypertonia and leads to a difficult evacuation. While it is not completely clear whether the hypertonic sphincter predisposes the patient to the development of a fissure (and/or symptomatic hemorrhoids) or is caused by the disease, the relationship between these two organic conditions is defined [17].

Anal fissure has usually a difficult healing and a high rate of recurrence. The main reason for chronicization of anal fissures is thought to be secondary to hypertonicity or spasm in the internal anal sphincter, which leads to local ischemia from lack of blood flow [18]. Treatment of anal fissures relies on reducing spasm in order to increase blood flow to aid healing of the fissure. Most effective treatments are based on resolution of anal hypertonia using drugs, mechanical or surgical dilation or sphincterotomy. If increased resting anal pressure is not adequately treated to reduce spasm, a difficult healing and enduring or recurrent anal pain will be obvious consequences [19].

Anal stricture is an uncommon condition defined as narrowing of the anal canal. Ninety percent of cases are the result of aggressive hemorrhoidectomy [20], but the condition may also be considered as a long-term complication caused by any condition that leads to scarring of the anoderm: chronic fissure, anal trauma, anal canal localization of an inflammatory bowel disease, chronic laxative abuse, radiation, and venereal disease. Patients usually report painful or difficult bowel movements along with rectal bleeding or narrowing of stools. Patients with a mild stricture may achieve relief with fiber therapy, daily anal dilation, or sphincterotomy. For patients

with more severe disease, treatment focuses on anoplasty with mucosal flaps or skin flaps [21, 22].

Another common cause of structural anal pain is the presence of a **cryptoglandular anal abscess**, especially during the formation or the recurrence of abscess and in presence of an unrecognized deep postanal space fistula after a horseshoe abscess, resulting in an internal sinus tract without any holes outside of skin [4]. These fistulae are not easily recognized on physical exam. Signs include pain between the posterior anus and coccyx. They can frequently be confused with puborectalis spasm that also produces tenderness with posterior pressure. In these cases combined approaches of endoanal, transperineal, and, in women, translabial/transvaginal ultrasound aided with three-dimensional capability proved highly valuable in clarifying the etiology of anal pain [23]. When unsure, also pelvic MRI may help diagnosis [6], it is particularly useful as a noninvasive method of excluding severe neoplastic conditions as cause of anal pain [5]. Spontaneous or surgical drainage of abscess usually leads to a sudden anal pain disappearance.

Chronic nonfunctional anal pain could also be present in FKT/orthopedic disturbances like **coccygodynia** or **lumbar herniated disc**. **Coccygodynia** is usually located or evoked by palpation of coccyx and it is resulting from previous coccyx falling trauma (also after many years from trauma). In some cases these patients underwent partial coccygectomy, with an 80% satisfaction rate but a complication rates nearing 50% after procedure [24].

Chronic anal pain is frequently defined as **pudendal neuralgia or pudendal neuropathy** and commonly related to pudendal nerve entrapment in pudendal Alcock's canal (***Alcock's Syndrome***). Nevertheless the literature pertaining to true incidence, diagnosis, and treatment of this syndrome is based on low-quality studies and controversial [25–27]. A 2008 meeting of pudendal neuralgia experts stressed that the pain is not nocturnal, and it usually gets worse with sitting (caused by nerve stretch). The panel also agreed that a pudendal nerve entrapment is more probable if the pain is relieved by anesthetic infiltration of nerve. Nevertheless the ultimate conclusion of the panel is that the only way to confirm the diagnosis is surgical exploration [28].

When anal pain is correlated to menstruation, irradiated to vagina and no anal diseases can be pointed out, also **endometriosis** of recto-vaginal septum must be considered. Bidigital palpation and ultrasound transvaginal evaluation can be used to confirm diagnosis, when endometriosis of septum is suspected [29, 30].

In female patients with previous pelvic surgery also a perineal **mesh erosion** should be considered and in male patients a **chronic prostatitis** should be taken into account.

The presence of a **Fecaloma** (especially in elderly and chronically constipated patients) or of a **foreign body** in the rectum can be considered as less frequent but not rare cause of nonfunctional anal pain especially when recently arisen. Retained rectal foreign bodies are a common presenting complaint to the emergency department, most of which are placed during sexual activity [31]. Despite the frequency of this presentation, the existing literature is sparse in terms of epidemiology, incidence of consequent rectal injury if ignored, and the need for surgical intervention [32].

Many other infrequent conditions can induce chronic organic anal pain and must be taken into evaluation. A **fungal infection** may create mild but prolonged pain that is less severe than an abscess. An ignored **anal cancer** can produce progressively worsening pain. An anorectal **sexually transmitted disease**, such as gonorrhea, chlamydia, or usually herpes, can cause pain and serous/mucus discharge. **Proctitis**, either primary or secondary to inflammatory bowel disease or after radiation, is also a cause of anal pain. Another rare cryptic source of anorectal pain, usually recognized on proctoscopy or colonoscopy, is **solitary rectal ulcer** [4].

9.3 Functional Chronic Anal Pain

When chronic anal pain is recurrent or persistent, with no clear structural demonstrable lesion and associated with urinary or defecation-related disturbances, a functional pelvic problem has to be considered especially if associated with impaired quality of life, anxiety, and depression [33]. In many cases it remains a diagnosis of exclusion. Its approach, diagnosis, and management still lack a standardized protocol [AF].

Functional symptoms usually involve voiding or defecation disturbances with disorders of the urinary bladder (i.e., chronic prostatitis/cystitis, interstitial cystitis, painful bladder syndrome, or Fowler's syndrome), reproductive tract (vulvodynia and/or dyspareunia), and the pelvic floor musculature (i.e., proctalgia fugax or the levator ani syndrome) [34].

In a suspected functional disorder **anorectal physiology testing** (if executable) could be useful. Anorectal physiology testing should begin with *anorectal manometry* measurements. If the measured pressures are high, a functional disturbance (such as anismus, proctalgia fugax, levator ani syndrome, or myofascial pain) should be speculated. Thereafter, an *anal/perineal electromyography* (*EMG)* testing can be performed to determine whether a paradoxical contraction of puborectalis during squeezing is also present.

Based on the Rome IV Criteria functional anorectal pain disorders are categorized into three conditions: levator ani syndrome, unspecified anorectal pain, and proctalgia fugax [3].

Different symptoms and clinical characteristics can be found in these three conditions related to functional anorectal pain.

Levator ani syndrome (LAS) is often known by many other names including anismus, levator spasm, paradoxical contraction of puborectalis, and chronic idiopathic proctalgia. The pain is constant or frequent, it can last many hours. Patients frequently describe a vague, dull ache, or pressure sensation in the rectum. It is often worsened with sitting, and it sometimes improves with standing or lying down. The pain is often reproduced with posterior palpation of the puborectalis muscle [2, 35] and it is associated with tenderness to palpation of the levator ani muscle [36].

In LAS noncontrolled studies have implicated an important role for pelvic floor muscle spasm, with increased anal resting pressures [37] and dyssynergic

defecation, which is characterized by rectoanal incoordination during defecation. In addition, these patients frequently fail balloon expulsion testing and have paradoxical contractions of their puborectalis.

Pelvic floor dyssynergia is the functional aspect of different pelvic diseases usually due to the failed, incomplete, or paradoxal relaxation of the puborectalis muscle. Physiological mechanisms responsible for LAS and dyssynergic defecation are similar. Eighty-six percent of patients with a highly likely diagnosis of LAS failed to relax pelvic floor muscles (i.e., to decrease anal canal pressures) when straining to defecate and 87% were unable to evacuate a water-filled balloon [38]. LAS and dyssynergic defecation appear to represent different symptom manifestations of the same underlying disorder. It not only depends on the isolated movement of the levator ani, but also on its active interaction with many other structures such as the diaphragm, the vertebral column, and the abdominal wall [39].

Some women with anal (and vaginal pain) may be suffering from **myofascial pain dysfunction syndrome**. It is characterized by severe chronic pain elicited by pressure over specific perineal trigger spots other than the posterior puborectalis, with and without dyspareunia. Separating the two is very difficult; for this reason some authors question the distinction between these entities [4].

Patients with the levator ani syndrome often have **psychosocial distress** (e.g., depression and anxiety) and impaired quality of life (QoL) [40]. Long-term pain can inevitably cause psychological disturbance. Depression is more common and severe in patients with functional anorectal pain and some researchers reported that depression occurs in about 30% of them [41, 42]. It is difficult to draw a conclusion whether pain precedes psychological disturbance. The causal effect between pain, depression, and anxiety still needs to be determined in future studies. However, it was previously conveyed that functional anorectal pain is affected by behavior and psychological factors [43]. For these reasons they must be taken into account in a comprehensive therapeutic algorithm when we approach these patients.

In **proctalgia fugax**, pain is brief (from many seconds to some minutes), intense (which can range from uncomfortable to unbearable), and sharp. It occurs infrequently (i.e., once a month or less often), usually unexpectedly and not related to defecation. Many patients are awoken from sleep because of the sudden onset of sharp anorectal discomfort, and earlier literature on the condition refers to it as "nocturnal proctalgia" [37]. Patients often deny anorectal pain between episodes.

In proctalgia fugax, the short duration and sporadic and infrequent pain episodes have limited the identification of physiologic mechanisms. Excessive colonic and anal smooth muscle contraction [36, 44] have been observed. Hereditary proctalgia fugax is associated with constipation and hypertrophy of the internal anal sphincter [45]. The episodes of pain are so brief and infrequent that remedial treatment is impractical and prevention is not feasible. However, defecation and self-digitation of the anus are reported to help with pain resolution [46].

In **unspecified anorectal pain** the patients suffer from chronic or intermittent pain with prolonged episodes of many hours. Usually it is not associated with tenderness to palpation of the levator ani muscle. Patients who don't report tenderness on digital palpation usually show relaxation of pelvic floor muscles when straining,

and most were able to evacuate a water-filled balloon (simulated defecation). There was also a striking difference in the responsiveness of these patients to all treatments considered: these patients reported significantly not to benefit from biofeedback, EGS, and massage. Thus, the distinction based on whether patients report tenderness on digital palpation is an important one, and clinicians have to consider this physical sign a requirement for the diagnosis of LAS or unspecified anorectal pain and for indication to biofeedback treatment [38].

Specific diagnostic/therapeutic algorithm have to be followed in these patients with suspected functional causes of anal pain [4, 46, 47].

Many treatment modalities have been proposed to treat this very challenging, disabling, and frustrating disturbance. The theoretical goal is to relax the puborectalis spasm, which is postulated to cause or perpetuate the pain. They comprehend: physical therapy with digital massage of the puborectalis muscle, biofeedback to teach patients how to relax the puborectalis muscle [48, 49], intrasphincteric/intralevator muscle injection of Botox to relax the puborectalis muscle spasm [50, 51], steroid caudal block and trigger point injections with a mixture of triamcinolone, acetonide, and lidocaine, and finally sacral nerve stimulation with unfortunately very datable and discussed results [52–54].

Treatment modalities to deal with functional chronic anal pain and their results will be discussed in more detailed and extensive way in other parts of this book.

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Mind and Pain: Psychotherapy and Hypnosis in the Treatment of Chronic Pelvic Pain

10

Walter Comello

> We cannot solve our problems with the same thinking we used when we created them.
> —Albert Einstein

Saint Augustine wrote: "*There is a myself inside me that is much more myself than I am*". Nobody better than him has summarized so simply a truth that can explain the extraordinary, though often difficult and conflicting, relationship between an individual—or what he acknowledges as himself—and a part unseen by his conscience. This second part was subsequently called the unconscious by Freud. It has an apparently untameable instinct, but it is often united to a reasoning that is difficult to decipher. Yet it is a logic, indeed Machiavelli would have called it a *reason of state*, which becomes a very powerful and incontrollable action on the rational conscience. And this action is responsible for 95% of the potential for action and thus for behavioural decisions, but it can also influence the individual's somatic aspects. The part we all identify with, the *I* with its cognitive rational functions, is left with very little power when it clashes with it. So, the educational and cultural actions—that, at times, the individual pursues for an entire lifetime in order to achieve self-control—don't succeed unless there is a meeting, a secret attempt to compromise that can lead to a fragile and temporary acceptance. It would be better for the meeting to be an encounter in which to familiarize and find the best solution. It is from this relationship or absence of one that behaviours stem from, and even the attitudes and words that can caress or wound. It is difficult to acknowledge the power of what we are to them, yet they are the containers of meaning that mostly invisibly and silently over time form that *myself inside me that is much more myself than I am.* Not necessarily objectively, but on the basis of the mind's attributing dynamics which give meaning to those words. There are words that hurt and words that heal, however none will be indifferent to the individual's experience. The only

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ones to be acknowledged by the conscience for their effects are those that caress or cut like a scalpel. Words are conventional codes among individuals who speak a shared language, but they get translated by the mind into images based on subjective experience. Previous experiences provide a short-term or long-term memory tank which the mind refers to for subsequent attributions. Therefore, the individual becomes and is the result of personal history by sum or subtraction of events. Culture worldwide, in the many diverse forms of languages and traditions, both vertically over time and horizontally geographically, has always used and still uses rituals and metaphors for its most powerful pedagogic, educational, management and thaumaturgic actions. A metaphor transforms words into images, it is carefully, strategically and powerfully chosen, never by chance, so that the mind can receive it easily by penetrating the cerebral cortex or activating the limbic system directly. A metaphor is the parable, the history, the fairy tale, the aphorism. A metaphor is a place, a gesture, an object, a white coat. Western culture over the last centuries has wrongly believed that all this together with individual life experience could *perhaps* be related to human behaviour, but not to the body. Not long-ago, medicine students during their exams would discuss neurons as being typical brain cells which, once degenerated, could not be revitalized. However, we now know that there are 500 million neuronal cells in the intestine. This is the enteric nervous system, also known as *second brain*, as defined by the Columbia University scholar Michal D. Gershon. The intestine contains millions of cells and neuronal fibres that constitute a real and true autonomous nervous system. It is independent of the central nervous system and promotes intestinal contractions as well as releasing digestive enzymes. The enteric nervous system can integrate and process both external and internal stimuli received from the body by interacting with the central nervous system through an exchange of information mediated by the psycho-neuro-endocrine-immune system, the release of hormones, the vagus nerve and the immune system. Consequently, the two brains influence each other and determine our state of psycho-physical well-being. In fact, mental stress and negative thoughts activate the circuits of anxiety and fear, thus provoking an increase of intestinal motility, the release of cytokine as well as increased sensitivity and inflammation of the intestinal lining. This can lead to, for example, the onset of the irritable bowel syndrome or of an intestinal inflammatory disease. On the other hand, states of intestinal phlogosis determine an increase in the production of serotonin, the good mood hormone, and consequently of the enzyme in charge of its demolition. Under these conditions, there can be a lack of serotonin at central nervous system level and an onset of depression.

The enteric nervous system uses more than 30 neurotransmitters, many of which are identical to those present in the central nervous system, like acetylcholine, dopamine and serotonin. More than 90% of the body's serotonin is located in the stomach, which contains also 50% of the dopamine—currently being studied to better understand its use in the brain. Therefore, there is a correlation between the *two brains* also within processes that are functions of the central nervous system, where the latter becomes an *influencer* of the first. Actually, it is more appropriate to state that there is a reciprocal exchange in which the vagus nerve acts as a bridge and

distributes the information to the body. This means that an individual's experience doesn't remain only within behavioural areas of competence, but somewhere in some way it acts on the body, certainly not randomly. And what happens in the body has an important effect on the individual's psyche.

All of the above, which could be much further expanded, is necessary to better understand and assess **the effectiveness of psychotherapy with the aid of hypnosis in the treatment of the pain symptom in patients suffering from chronic pelvic pain** (CPP). In this chapter preconditions, protocol and results of treatment of CPP with *a specific psychotherapy method, which uses hypnosis* for a 6-month period, will be discussed.

10.1 Study Preconditions

There is a known correlation between CPP and the psychological condition experienced by the patient. On the other side, clinical hypnosis is recognized as having a role in the treatment of pain

10.2 Materials and Methods

Thirty-two patients (26 women, 6 men), average age 36.2 (21–52), affected by CPP clinically diagnosed and already treated with conventional therapies following the guidelines were selected. All shared the persistence of the pain symptom regardless of the conventional treatment (lifestyle, oral therapies, intravesicular therapies).

Before psychotherapy began, all patients underwent a standardized set of tests validated on the Italian population.

Tests administered:

- Cognitive Behavioural Assessment (CBA)—The test aims to collect all the data required to identify appropriate modalities of psychological activity for the symptoms described by the patient. It includes ten sections, each containing homogeneous items that investigate a specific aspect of the subject. The questionnaire collects and processes all the information including it in a wide-ranging assessment of the person's past and recent history. It thus produces a general personality profile.
  - Sexual Evaluation Schedule Assessment Monitoring (SESAMO)—A psychodiagnostic test which explores sexual and relational aspects, both normative and dysfunctional, in subjects that are single and not. It produces a psychosexual and socio-affective profile of the person as an idiographic image. It also formulates hypotheses on the causes and the dysfunctional aspects within the individual's and couple's sexuality. The investigation regards essentially the areas involving remote and current sexuality, but at the same time it also considers those connections that, even though indirectly, may have influenced

the formation and expression of the personality, of the affectivity and relational style.
- Minnesota Multiphase Personality Inventory 2 (MMPI-2)—One of the most widespread wide-range tests used to evaluate the main structural personality characteristics and emotional disorders. It is composed of 567 items, grouped in validity scales. The basic ones investigate the most significant personality aspects, the supplementary ones help to better understand any difficulties or disorders that emerged. In this version, more validity indicators have been added as well as additional scales. Also, norm standards more representative of the Italian population have been included. And the items have been formulated to eliminate ambiguity and gender discrimination.
- Stanford scale of hypnotic suggestibility—It's the most well-known scale of hypnotic suggestibility and consists of some suggestion-tests that are administered together with a standard hypnotic induction process. It is useful to assess the individual tendency/susceptibility towards the hypnotic process and highlights different responses to treatment.
- Quality of Life Index (QL index)—A very simple and short tool (5 items) designed to evaluate the outcome of treatment for cancer patients. However, as it's very general, it can be used also for other pathologies. It explores activities, daily routines, health, support and emotional states as well as providing a global assessment of the evaluator on the accuracy and reliability of his evaluation. The test offers a valid reference point for assessing treatment risks and benefits.
- Visual Analogic Scale (VAS) before and after treatment—This tool measures the subjective characteristics of the pain experienced by patients. The guidelines on pain treatment in the traumatized highlight how this symptom is often relegated to being second class and confirm the opportunity of adopting scales and tools that measure patients' subjective perception of pain in order to treat it more adequately.

Patients attended a 6-month therapeutic treatment with weekly appointments.

10.2.1 Phases of the Psychotherapy Process

- Search for a remote cause-effect diagnosis previous to the clinical diagnosis
- Evaluation of how the cause-effect relations identified concern the time of symptom onset or its current existence, for a current diagnosis.

These diagnostic phases are also part of the therapeutic process for the patient.

- Approach and training for the use of hypnosis based on a specific non-inductive method that aims to overcome unconscious patient resistance.
- Therapy using hypnosis with a body orientation to intervene on symptoms and symbolic implication to dematerialize the cause-effect relation.

10.2.2 Outline of the Psychotherapy Process

- *The body district is explored with its functions and meanings in a psychosomatic perspective*
- *Symptoms' time of onset*
- *Patient experience of the symptoms' onset*
- *Patient's subjective interpretation of the symptom–pathology*
- *Symptom structuring dynamics*
- *Hypnotic therapy*

10.2.3 The Body District Involved in the Psychosomatic Perspective

The urogenital apparatus is a complex system that oversees the excretory and reproductive functions. It refers to identity, male or female, to sexuality and related experiences, to the meaning of maternity. The excretory functions relate to the subject's dynamics concerning *acceptance or non-acceptance*. Additional meanings stemming from culture, education and life experiences may also be involved.

A subject not always welcomed, but of great interest when desiring to understand the reasons for a pathology's onset in a specific area of the body, is that of what organs symbolize. The world's culture, over time and across geography, seems to have a shared and recurring vision. This is what rituals from far away worlds and languages with their slang or local idiomatic expressions refer to. So, for example, organs like the heart and the liver seem to be always and everywhere considered, from the most archaic cultures to the skyscrapers of New York, one the centre of goodness and love and the other the centre of courage.

In an isolated Benin village in Africa, hundreds of miles away from the Guinea Gulf, a king had died. To celebrate his funeral hundreds of people from all the nearby village had come, with their kings and *fetisher* or shamans, who represent and at the same time interpret the religious and thaumaturgic power, as well as magical beliefs. The king had seven children and for this reason seven cows had been butchered and their meat distributed to the population. The carcasses were brought to a sacred spot near the village where only the kings and *fetishers* gathered. The dead king was renowned for his goodness and courage, and therefore for this specific ritual, the hearts and livers of the cows had been extracted. The kings and *fetishers* shared and ate the organs, so that by bringing them inside themselves they could also share the goodness and courage of the dead king.

Therefore, courage seems to have a location, a specific organ, the same of anger that is at times so difficult to contain. The heart instead appears to be the centre for goodness and love. For a long time, we've known that a healthy sentimental life is a base for the body's healthy functioning, starting from the immune system, and how much it affects cardiovascular diseases. This is true also when, in the absence of a partner or children, affective emotional needs are met by a pet. Probably science will soon be able to relate the more recent discovery of 50 million neurons in the

heart with the influence that our sentimental life has on the central nervous system's decisional processes.

Body organs have physiological functions but also symbolic ones. Indeed, their symbolism derives directly from their physiology. This mind body relationship is at the origin of well-being or pathology. Just like life quality is subjectively—and not objectively—an important condition for the organism's health, its negation can prepare for the onset of an illness that can be physical, psychic or both. So the arrival of a disease should not be interpreted as a casual or unlucky condition, but as the specific expression of an experience not casually referred to a target organ exactly because of its specific functions. Therefore, chronic pelvic pain is not only expression of a body that by chance—and for unknown reasons that there is no point in searching for—at a given point in life manifests itself. On the contrary, it is the clear symptom of a lifetime that for a specific reason represents itself in that body district and exactly with those modalities. The pathologies examined within chronic pelvic pain will presumably have a series of possible foreseeable origins, always and only related to the patient's subjective, and not objective, experience. The different diseases will differentiate in terms of symptoms and original causes, but with shared denominators. Interstitial cystitis will have shared roots, like endometriosis and pudendal neuralgia. A remote diagnosis within the patient's experience, in coherence with contemporary clinical diagnosis, is the essential condition for planning psychotherapy and for symptom resolution.

10.2.4 Chronic Pelvic Pain, a Different Interpretation

Chinese medicine defines the bladder as the soul's mirror.

A pathogenic agent acts on a terrain that has been predisposed by a specific psychological conflict, recent or remote. Possible consequences are *the pain and burning as an expression of an unhealed* wound, necessary at the time and that must continue to perform its sanctioning, avoiding and/or attentional function. It can then be interesting to discover fairly often a different meaning of the pain with respect to the burning within the patient's experience. The prior occurs more often in patients who seem to have sanctioning motivations related to past experiences that no longer exist in this somatic expression. Pain redeems from faults, indeed in the Bible Christ died on the cross to save humanity from the original sin, in other religions pain is a direct route for a certain Paradise. Burning instead relates to internal judgemental and guilt inducing dynamics where the burning is the means used to stop oneself, a tool for avoiding behaviours considered inadequate. This is the result of the *frequent urinary urgency that forces social isolation and justifies both with oneself and others the non-action.* The dynamics of control and non-control are definitely important, but they're subordinate to an unconscious and unaware need to yield to the seduction of fragility. Fragility absolves and creates *safe harbours* even where healing appears and is affirmed as a need. Often words, exhausting requests for help and at times even tears are not a priority compared to unconscious or veiled awareness of keeping the problem alive. Therefore, the reasons for maintaining the symptoms in this case risk being stronger than those for healing them.

10.2.5 Time of Symptomatology's Onset

The initial sessions with a patient aim to search for the onset of the first symptom over time and within memory, as precisely as possible: year, month, day and moment. Often repression processes and previous patient interpretations can compromise this search. The symptoms could have multiple forms at the time of inquiry or could have had them over time. It will be necessary to define the evolution of each symptom and to place it at a precise moment of the patient's history. It is important to return to the first symptom and to the time of its initial occurrence. From here an analysis of the patient's feelings related to the symptom's onset and the remote diagnosis begins.

10.2.6 Patient Experience in Relation to the Symptomatology's Onset

A single event, or episodes that repeated or spread over a timespan that can even be years, or is existent in the patient's current life is sought for. It will be an event emotionally important, in a nearby moment or at a time occurring at the most within the last year. A year is a conventional measurement unit in which past moments that could be at the origin of the symptomatology recur or are evoked. It is more likely that the causal relation will be of weeks or a few months. The event to look for isn't necessarily traumatic, even though patients often tend to concentrate their search on this kind of situation. It is an emotionally important event and, in the absence of trauma, it has the force to recall a remote trauma. This occurs unconsciously, but with a strategy aiming for the target organ. The unconscious will act similarly to a *magician* facing his audience: it will create a suggestion, a presumed different reality protecting the hidden truth. The goal is the effect, the symptom that precisely with its characteristics expresses its aim. *The magician* will be able to act successfully for years, but will stop being effective once *his trick* is understood. His effectiveness will increasingly lose power as the patient understands and accepts the cause and effect dynamics. It will then be important to observe the changing characteristics of that specific set of feelings over time. This is the purpose of psychotherapy: producing awareness, a new awareness as a basis for change.

10.2.7 Patient's Interpretative Subjectivity of the Symptom–Pathology

The patient's pathology can be diagnosed as a *post-traumatic stress disorder* in which, as widely shown by many studies, what counts is the subjectivity of events and not their objectivity. Albert Einstein affirmed that *a new way of thinking is necessary to solve the problems created by a previous way of thinking*. Before starting this specific psychotherapy, the patient has walked different therapeutic roads and

each one has surely conditioned and influenced his attitude and his willingness to finding a solution or even searching for one. The longer he or she has suffered, the less trust in finding a solution there will be. The longer the person has thought there not to be a causal connection in his symptoms, but only an unfortunate organic coincidence, the longer it will take him to accept its existence. The more traditional therapies have been the only option considered, the more it will be difficult to believe in a possible solution, although he can't do without one with his symptoms protracting over time. In some cases, patients have tried alternative solutions that were alternative only in the modality and brought no results. In other cases, patients for their culture or experience consider cause and effect relationships that have no foundation and thus are useless for healing.

The initial psychotherapy sessions will aim at building trust in its being a new and valid tool that is based on concrete principles, science and results. A new way of thinking prepares the patient to trust the therapeutic process. He will discover a causal and non-causal relation in which he identifies authentically and this will lead him to fully understand the therapeutic process. It is important to understand but it isn't the solution. After a few integrative and strengthening therapeutic settings, the patient will be willing to make what he has understood into his understanding. There is a fundamental difference: understanding means to take within and what you bring inside has the force for transformation. The dynamics that led to the illness had it, with similar competence the healing dynamics will have it too. If for some reason by now clear in the patient's experience the mind created his symptomatology, if there are no longer any reasons for it, the mind will gradually influence not creating the symptoms anymore. Hypnosis will be the tool able to access that competence area surgically, and from that time on will be perceived by the patient as relieving of responsibility in respect to the solution. It is essential to observe if the causal relation is maintained during psychotherapy by symptom structuring dynamics such as sanction, avoidance and attention. In this case, the following psychotherapy sessions will investigate them further in order to extinguish them. Until this condition is fulfilled, there will be no solution and even hypnosis will be useless.

The problems arise from *devaluing circumstances occurring over time or never realized* in the patient's evolutionary process.

They can be traced back to:

- *Sexuality experienced as guilt-inducing or accomplice* following child abuse often within the family
- *Homosexuality* not accepted or experienced conflictingly
- *Gender identity conflicts* and corresponding difficulties with cultural acceptance
- *Paraphilia* causing non-acceptance and conflicts
- *Emotional abandonment* causing devaluing conditions of the gender identity
- *Unresolved conditions relating to motherhood* following abortions, difficulty to procreate, severe unease in the relationship with one's mother in an identification-projection mechanism of a daughter.

10.2.8 Symptom Structuring Dynamics

Often the remote diagnosis in its cause-symptom relationship, together with the absence of prejudice, is the premise for the awaited use of hypnosis. This will lead the patient to recognize himself concretely in his results. In other cases, the analysis of the symptom's structuring can be the most difficult part for the patient. Acknowledging that there is a resistance towards healing isn't easy to accept and for this reason it is also hard to understand. But psychotherapy will proceed quickly reminding the patient of Hippocrates's phrase: *before healing someone it is necessary to ask if they are prepared to let go of what made them sick.* The patient will be able to recognize the reasons of his resistance and will then be prepared to face them. Psychotherapy will provide the tools or will suggest replacement alternatives if necessary. Both the onset and maintenance over time of the symptom–pathology serve for one or more of the following conditions: *sanction, avoidance and attention*.

- *Sanction—in guilt-inducing experiences where the pain or pathology are the means for atonement, precisely in the body area considered target organ deserving the specific sanction.*

The invalidity brought by the urinary frequency, the social unease caused by interstitial cystitis, the pain of pudendal neuralgia and endometriosis all refer to men or women who, for reasons buried over time, believe they are guilty of actions, or accomplices of others' actions, for which they deserve sanctioning. Their actions are always evaluated by a sort of *inner judge* that speaks using the inner voice, a severe *prosecutor* gripping a sacred text that contains values, culture, education, ethics, in other words what Freud would have called the *Super ego.* His only goal is to highlight faults and request the maximum possible penalty. The penalty can be physical pain, unhappiness or both. Depending on the assumed severity of facts the judge will sentence *the defendant* to atone by targeting the specific guilty organ for a timespan considered right and proportional. This period may last years or an entire lifetime, and in the most severe cases can lead to death. Death can occur either when a more serious life-threatening illness develops or with the person's suicide. Pain becomes a constant daily experience that has no respite. Sometimes the pain is only in the body, often invalidating the person in many aspects of his life quality and even undermining it completely. The target organ is subjected to a kind of *law of retaliation*. Cultures in which this is standing legislation derive it from a profound feeling of individuals: the kleptomaniac will attribute the whole responsibility of thefts to his hand, thus absolving his conscience and even lucidly recognizing it as correctly behaving. There are people responsible for serious crimes who seek their acquittal—or facilitated treatment—when approaching a real judge's sentence by attributing to an alter ego, a foggy state of conscience, the entire responsibility of that terrible gesture. They claim that those behaviours would never have been committed lucidly. There are subjects who in life attempt to escape their responsibilities and

others that through their symptoms or pathology acknowledge or even enlarge them, or take them on without guilt. However, the attribution of blame—whether real or not—is an unconscious process, and their somatization originates from here. All this will hold even more when rationality tends to attribute the origin of the disease, of all symptoms and their consequences entirely to organic causes. The cognitive rational mind enacts defence mechanisms that free from responsibility and entrust exclusively the medical specialist for the solution. From a psychotherapeutic perspective, the solution lies in the use of metaphor suggesting a sort of *therapeutic appeal court* in which to search for a sentence that differs from the first instance one. The psychotherapist will resemble a *defence lawyer*, but will most of all be a new *expert consultant* which provides the judge with a new version of the facts. So, therapy sessions will see a confrontation between on the one hand the new *defence approach* and on the other the patient in the roles of defendant, prosecutor and judge. *A different trial result will come from the re-examination of facts, from general or specific mitigating circumstances that will lead to acquittal.* Consequently, the body will no longer receive the sanction because the subject is rendered free of guilt. From that moment onwards, unless the patient has other reasons for structuring the symptom, hypnosis can be used to gradually reduce or totally heal the symptomatology.

- *Avoidance—as a tool to subtract oneself from the what is undesired, feared or towards which one feels inadequate or considers to be above personal abilities*

While the prevailing symptom of sanctioning is pain, in avoidance it is burning, and in the case of interstitial cystitis it is the urinary urgency. Within the avoidance dynamics of CPP patients, symptoms become functional to prevent or justify a condition. They are functional in an unaccepted—though desired—behaviour enacted by the subject or by others towards him. In other cases, it serves to avoid or restrict the undesired behaviour of others towards the patient. It often comes from a sexuality experienced as unacceptable, though perceived with a strong feeling of attraction. The strongest transgressions, like desires at times unconfessed even to oneself or fantasies that must be stopped before they turn into action, find a management tool in pain. A true *hell inside the body* flames that inhibit pleasure. As usual it is the subjectivity and not necessarily the objectivity that activates this symptom. The burning will be functional to avoid a sexuality perceived as guilty or accomplice, gender identity conflicts, paraphilia. A conflict between instincts and ethics, between the Id and the Super Ego that compromises the ego. In other cases, the burning serves to protect the subject from an emotional investment which appears risky or strongly destabilizing of psychic stability. The patient will tend to deny, to obstinately hide his condition to himself, often declaring in opposition the sincere desire for a new bond. It will be easy to find within the subject's history a significant pain caused by abandonment or betrayal. A truly *burning* disappointment that becomes *fire* like his symptom. If sexuality is often the engine in building a couple, the burning in that specific area becomes the best inhibitor. The same symptom appears also

as the negation of behaviours others enact towards the subject, in those cases where a fragile personality cannot prevent them and is forced to endure the action of an undesired partner. In this case, the symptom is actually a request to the subject to find the courage, the force to deny himself and thus remedy the situation. In every case the avoidance mechanism is functional to those who consider themselves unable to refuse. The psychotherapy process will have to find a solution, first of all acknowledging the issues at stake and then finding alternative strategies. Subsequently, hypnosis will play an important role, but only once the patient is authentically motivated to resolve.

- *Attention—in those subjects who discover the effectiveness of their symptoms for attracting the interest of family members or loved ones considered inadequately attentive.*

Attention is the measurement unit of love. It's one of the first learning experiences in life, the same that one risks to use in every occasion for the rest of one's life. When a baby is newborn, he discovers that his intense crying is irresistible for the mother who will soon arrive and take him in her arms. The mother will behave in this way believing that she is responding to her baby's need and the baby will discover that the mother's body is warm and soft and her milk is sweet. In that moment, he discovers that his crying is an effective tool for obtaining those conditions, and every subsequent time will confirm this. He doesn't fully understand the process, but he perceives the well-being which derives. His tears obtain attention which leads to well-being and his understanding is that it is an act of love. From that moment onwards every child, and subsequently every adult, will be aware of this and be able to use it throughout life. Tears will become the means for the somatization of discomfort, and both produce attention. There will be many occasions to manifest that discomfort to initially attract the mother and then, in the future, a partner. At times in the absence of a partner, or even when there is one, the search extends to the patient's social life: to doctors or whoever performs health supporting actions, psychologists and so on. The invalidity and pain produced by the urinary urgency are often associated and they reinforce each other precisely when they take on parallel effectiveness: the former as attention seeking and the latter as avoidance. At times the need for attention isn't characteristic solely of subjects who've made it their way of life, in any case it will seduce those who've always taken care of others' needs. Sometimes attention seeking is a need that is addressed to oneself, particularly in those people who need to remove it from the too many responsibilities or commitments they've undertaken in their lifetime. Psychotherapy will have to lead the patient to acknowledge this need and this often-unaware functional action. An essential condition for the patient to stop using this mechanism is a therapeutic strategy, which can include compensatory dynamics, that will conduct the patient to realize that merit rather than need will bring that attention—love.

The solution of symptoms and pathology requires the extinction of whatever maintains in being all three conditions.

10.2.9 State of the Art of the Psychotherapeutic Work

The patient's therapeutic process has so far included:

- *The search for a* ***remote cause-effect diagnosis*** *previous to the* ***clinical diagnosis****.*
- *An assessment of how the cause-effect relations identified within the problems are related to the time of symptom onset, and of its current presence, for a* ***current diagnosis***
- *An analysis, recognition and extinction of the causes maintaining active the* ***symptom's structuring dynamics***

From this time onwards, the patient has *a new awareness* of himself, of his current condition, and also of the causal experiences that have determined his symptom–pathology. He recognizes the symptom's structuring dynamics, understands and shares the responsibility for a solution, a partial solution or a non-solution. *The solution* will be available to those patients who, after understanding the cause-effect relations, will not maintain them or the symptom's structuring dynamics alive. *The partial solution* will be for those patients who, after understanding the causal connections of their experience, will maintain the symptoms with a different frequency and/or reduced intensity, by not giving up completely the benefits deriving from their structuring dynamics. *The non-solution* will be for those patients who will not identify with the causal links between clinical diagnosis and remote diagnosis and will continue to believe their pathology to be exclusively organic. It will also be for those who, while acknowledging the causal links, consider the pathology functional to their life, see their illness as an alternative to relational choices believed to be impossible or that in any case they aren't prepared to make. At this point of the psychotherapeutic process the patient is already able to recognize a partial result or a non-result of his symptoms with respect to three parameters: *frequency, intensity and duration*. From now on the patient is ready to begin the final important part of his therapeutic process with the use of hypnosis. This will put him in a special mind-body relation that will enable him to measure weekly *his results*, in respect to the reference parameters, until the symptom's extinction or its important reduction. Once these results are reached, they remain irreversible even after the completion of the 6-month psychotherapy.

10.2.10 Hypnosis in Short

Hypnosis is a specific state of consciousness in which the natural analytic functions are sufficiently reduced to consent the use of deeper unconscious levels for the individual's well-being. It is an extraordinary medical and psychological tool increasingly used in different contexts. Every human being provided with normal psychic activity can access them and the use of this technique for therapeutic purposes has no side-effects whatsoever. CLINICAL HYPNOSIS does not envisage loss of

consciousness or memory, nor can it act in any case against values or models of the subject.

How it works: The level of consciousness passes from the state of vigilance to an apparent sleep state through an imaginative phase, going from a lighter trance to a deeper one. The borders between these states are not well defined. The person experiencing hypnosis always perceives a pleasant sensation of peace and relaxation, is aware of what happens and will remember everything once he reopens his eyes. Hypnosis is achieved with a monoideism, by maintaining an idea that transforms into psychic and physical condition during the experience and in a subsequent time following the trance. It is an extremely natural psychosomatic phenomenon.

What it's for: It is effective for problems based on emotional states and habits considered inadequate, it values individual skills, stimulates the immune system, intervenes evidently and in a clinically measurable manner in physical therapies.

Medical uses: alleviates or eliminates any kind of pain, to the point of being, in many cases, an incredible natural alternative to pain killers. Greatly effective in sexual therapies, it intervenes in a targeted way on every form of organic pathology by stimulating the immune system and working on the specific area psychosomatically.

Psychological uses: it eliminates anxiety, depression, phobias and compulsive behaviours. It overcomes dependencies such as smoking, alcoholism and drug addiction when there is true motivation. Hypnosis can also induce positive feelings, regulate eating behaviour and is very important in post-traumatic stress disorders. It always solves in harmonizing processes of self-esteem.

Creative uses: It is useful in the artistic and sports fields. It improves artistic performance by favouring greater attention and concentration, it increases muscular resistance and permits peak performance. It unblocks hidden potential, stimulates creativity and helps the anamnestic activity when studying.

Legislation: Hypnosis is an authorized and experimentally verified therapeutic method in use for over a century. In Italy, it is fully legitimated by the principle of therapeutic freedom and in the recognition by the scientific community. Hypnosis can only be practiced by those authorized to practice a health profession. In other words, the hypnotist must be a qualified doctor or psychologist or, when used for pain therapy, a dentist. In some states, it may be practiced by health staff adequately trained in managing specific protocols. Any other use with clinical, diagnostic or therapeutic goals by unauthorized people implies the crime of unauthorized medical practice, envisaged and sanctioned by the criminal code.

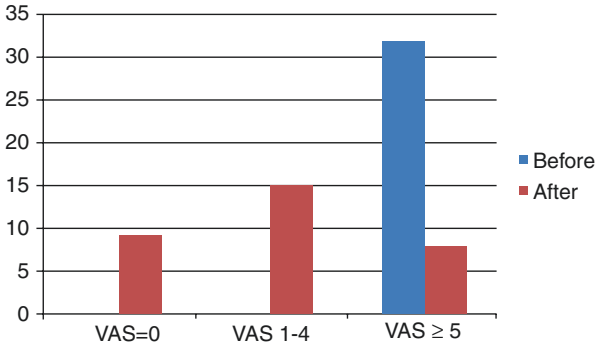
10.2.11 Hypnosis Therapy within a Specific Intervention Protocol

Hypnosis is taught to patients as a technique and tool for accessing a level of conscience useful for the goal planned and determined by a modular process and not using inductive techniques.

- Patients maintain a state of conscience and play an active and integrative role in the therapeutic process.
- Patients gain competence and awareness of their psychosomatic potential and from then onwards also in relation to the onset and the resolution of their problem.
- The contents of the psychotherapist's language are the essential key for the solution

Hypnosis is achieved through a psychosomatic phenomenon which deeply and authentically changes the patient's condition. The mind with its daily experiences is directly or passively responsible of our problems. The opportunity of understanding its reasons and extinguishing its cause-effect relations creates the necessary premises for the healing process. *When appropriately guided, the mind knows how to orient itself. It knows how to work on the body and heal it where necessary*. Those same skills that made it ill will know how to remedy to what was created once. It is a special state of conscience in which the patient conserves memory of what happens, it is not mind conditioning but removal of the obstacles that lie between disease and healing. It intervenes on the symptom- pathology, annuls pain and every session is a step forward, measurable and concrete, towards healing. Results are stable and irreversible because they are expression of a profound process of change achieved with a brief, silent and invisible process. These results are measurable by the patient first and consequently by the specialist through three evaluation parameters, *frequency, intensity and duration*. As the weeks of hypnotic treatment progress, the patient will gradually observe a reduced frequency of the pain or burning symptom, or of the urinary urgency. The patient will refer with satisfaction the progressive reduction of the symptom's intensity and notice that when the symptom does arise, it lasts less and less than before. Once these conditions have been reached (the remote diagnosis showing the causal relation between patient experience and illness onset, the removal of the symptom's structuring dynamics that kept it alive) by the psychotherapy, there are no insurmountable limits to the mind's ability to act on itself and on the body. The hypnotist's voice accompanies and teaches the mind to do what it already can do. His words are weighed and measured, surgical, like the precise action of a scalpel. So, they will be seeds that sprout a new condition. From the very first session, patients are accompanied by forms which measure results and variations in hypnotic suggestibility, by a protocol developed on the specific person and by forty-two parameters purposely studied. Time and clinical tests will then provide confirmation to patients of their results.

10.3 Results



10.3.1 Wh

Mean VAS score at the baseline was 8.15 (7–10), after 6 months 2.69 (0–8).

After 6 months VAS score was 0 in nine patients (28%), 1–4 in 15 patients (47%), >5 in eight patients (25%)

Mean QL index at the baseline was 3.31 (2–5), after 6 months 8.13 (4–10)

Improvement in standardized tests (domains of daily activity, sleep quality, social interaction, subjective perception of well-being) was also seen.

The results can be considered stable and without relapse or aggravation risks in that they have been produced through a gradual process of change induced by the psychotherapy's action. For the same reasons, they may be considered improvable even without psychotherapy. Two new interesting projects could be the follow up after a given timespan in absence of therapies (both conventional and psychotherapeutic), and a statistical analysis, based on conventional diagnostic parameters, of the personality types characterizing CPP patients—diversified for the three reference pathologies: interstitial cystitis, pudendal neuralgia and endometriosis.

10.4 Conclusions

This work shows how psychotherapeutic treatment with the aid of clinical hypnosis, within a specific intervention protocol, is an interesting research field for pain therapy in CPP patients.

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Microbiome and Chronic Pelvic Pain

11

Gabriele Bazzocchi, Mimosa Balloni, and Silvia Turroni

11.1 Introduction

The causes of chronic pelvic pain (CPP) are multiple and different according to gender and age. It is self-evident that in the presence of pathologies such as endometriosis, dysmenorrhea, myofascial pain syndrome, ovarian remnant congestion, pelvic congestion, pelvic fibrosis, pelvis neurodystonica, cancer pain, adhesions after surgical procedures, radiation proctitis, ureteral obstruction, and others, all causes of CPP [1], a possible alteration of the microbiota in the hollow organs of the pelvic cavity (digestive tract, bladder, urinary tract, prostate, and vagina) may be not particularly relevant. On the contrary, when the origin of CPP is comparable to "dysfunctional" conditions, characterized by alterations of function, phenomena of micro-inflammation and activation of cellular and humoral immunity, such as vulvodynia, interstitial cystitis, prostadynia, or irritable bowel syndrome, furthers causes of CPP, the involvement of the microbiome may be critical for the genesis of disorders. In other words, when CPP is comparable to a visceral pain, the most recent scientific evidence shows that its cause is often to be found in an alteration of the microbiome and its relation to the host. Visceral pain recognizes various pathogenetic mechanisms and, in particular as regards hollow organs, distension, paroxysmal contraction, hypoxia, and inflammation phenomena, which, as we will see, are all mediated by the interaction with the microbiome and the molecules it

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produces or contributes to, which have the potential to exert strong effects on the cells of the bowel wall whose structure and function are in turn under the control of the central nervous system (CNS), peripheral nervous system (PNS), and autonomic nervous system (ANS).

11.2 Microbiota, Microbiome, Metabolome

The term *microbiota* defines the set of symbiotic microorganisms that cohabit in the human organism without damaging it. It has almost completely supplanted the obsolete and less appropriate "microflora," a term that recalls the plant kingdom in which bacteria were once classified. Based on recent revised estimates, the human microbiota comprises approximately 10^{13} prokaryotes (bacteria and archaea), as well as fungi and viruses with a contribution of 0.5 kg of the average adult's body weight, but with an extraordinary metabolic capacity, far exceeding that of human beings [2–5]. Of all these microbial components, bacteria have been the most thoroughly studied, but it has become increasingly clear that trans-kingdom interactions are just as important in influencing health and disease [6]. Many if not all human cell structures coexist with a more or less rich microbiota: organs as the lung, or the bladder, not to mention the fetus, which until a few years ago were considered examples of "sterile structures and systems," in fact turned out to have their own microbiota, and in many cases some of their pathologies have been associated with alterations of its composition. That applies for example to all recent works that describe the role of urinary microbiota in urinary tract and gynecological dysfunction [7–9]. Not discounting a number of shortcomings in the available studies, even blood does not seem to be excluded [10], whereas the only exception, to date, is represented by the CNS. There is no doubt, however, that the microbiota residing in our gastrointestinal tract is the hub upon which the modulation not only of all intestinal functions, but also of other organs, depends, including the CNS, even at the level of its "higher" functions such as mood and ideation. Harboring around 10–100 trillion prokaryotic cells at density of 10^{11}–10^{12} cells/mL, the human gastrointestinal tract is one of the most complex microbial ecosystem on the planet Earth, comprising only a few phyla (Firmicutes and Bacteroidetes) but hundreds of species, thousands of strains, and millions of bacterial genes with specific assemblies for each subject, like fingerprints. Added to this is the high degree of plasticity, i.e., the microbiota ability to change in response to several endogenous and exogenous factors, such as age, diet, geography, lifestyle, intake of drugs, and host inflammation [11].

The term *microbiome* refers precisely to the whole genetic patrimony possessed by the components of the microbiota, i.e., all the genes it harbors and can potentially express. The tremendous and incredible impulse of knowledge on the richness of the human microbiota, the complexity of its interactions with the host and its consequent role in the onset and progression of many intestinal and extra-intestinal pathologies, which we have witness in recent years, has been possible thanks to our progressively increasing ability to typify the microbial genome. The

classical basic microbiology approach, based on the growth of biological material in special, but still limited, culture media, in fact could not give a complete and accurate description of the intestinal microbiota. This is due, on the one hand, to the huge number of strains present at a variable abundance in a single fecal sample and, on the other, to the difficulty of cultivating anaerobic microbes and reconstructing the existing syntrophic relationships between them, which make up the vast majority of the intestinal microbiota. The current gold standard to get a complete picture of the microbiota, in terms of composition and functionality, is represented by next-generation sequencing technologies, which fall into two main categories, i.e., targeted sequencing (of hypervariable regions of the 16S rRNA bacterial gene) for taxonomic purposes or whole-genome shotgun sequencing to retrieve information on all genes encoded, up to the assembly of whole genome. Until a few years ago, sequencing one million DNA nucleotide bases costed around US$ 10,000, which made the mapping of such a complex microbial ecosystem unaffordable. Between 2001 and 2011, as a result of major technological advances, the cost for the same test decreased to US$ 0.10, making it possible to define the compositional and functional structure of the microbiota in large populations of healthy and/or diseased patients [12]. It is thanks to such progress that we know that our symbiont gut microbial communities contain more than five million non-redundant genes (i.e., 500 times the human genome): through which microbes provide us with a range of otherwise inaccessible metabolic capabilities and play a fundamental role in training and influencing our immune system [13, 14]. However, it is also worth noting that a large amount of functional diversity is still largely uncharacterized ("the microbiome dark matter"), with potentially other important contributions to human pathophysiology.

Finally, the term *metabolome* refers to the complete set of metabolic products found within a biological sample, i.e., all the compounds that are likely to be involved in the biological processes of an organism. This includes both the substrates necessary for biochemical reactions, and the products derived from them, and hormones and other signal molecules. Like the microbiota, the metabolome is an extremely dynamic entity, which is able to change in a very short space of time: like all biochemical reactions, the modification of a single element can lead to a completely different final result. For this reason, no method of analysis can actually reflect a complete picture yet: metabolomic (i.e., the study of metabolome) indeed provides a partial snapshot of metabolism, also depending on the type of analytical technique used. Despite this, interest in this field has registered one of the most important scientific "revolutions" of the last decades. In January 2007, researchers from the Universities of Alberta and Calgary completed the analysis of the human metabolome, identifying and characterizing about 2500 metabolites, 1200 active ingredients, and 3500 components of food origin [15]. This enormous variability contributed by the microbiome, especially the intestinal one which, being at the connection between diet and host physiology, can produce and/or contribute to a vast range of bioactive small molecules virtually influencing all aspects of human physiology and biology [16–18].

11.3 Intestinal Dysbiosis and Its Functional Consequences

The human gut microbiome is typically defined by global ecological parameters such as richness, diversity, and evenness of its microbial communities: as nature teaches us, a high richness and diversity of species is an indicator of health of every ecosystem. In particular, a high biodiversity of the gut microbiome is universally recognized as a hallmark of intestinal health, being the guarantee of completeness, integration, and normality of the digestive, absorption, and nutritional processes that take place in the digestive tract, but that influence the health and functioning of all organs, brain in the first place. Conversely, reduced microbiota diversity has been observed in a multitude of infectious diseases, metabolic diseases, and inflammatory disorders. As anticipated above, the microbiome complexity and stability are influenced over time, from infancy to old age, in relation with many factors such as genetics, mode of birth, breast or formula feeding, geography and early childhood exposure, sex, age, hygiene, psychology/stress, diet/nutrition, physical activity, tobacco, alcohol, and drugs. In this respect, let's just think of the effects of prolonged and recurrent antibiotic therapies and the intake, often abused, of the Proton Pump Inhibitors (PPIs), which results in a zeroing of gastric acidity, a real entry barrier to food and drink microorganisms from the outside world, and therefore a very important physiological factor in maintaining the stability of the intestinal microbiota. In fact, all these factors may induce perturbations affecting the complexity and stability of the microbiome, potentially leading to *dysbiosis* [19, 20]. In practice, all aspects of behavior and interaction with the external environment have the potential to act on composition and gene expression of the microbial community: when the interaction between these factors severely compromises the biodiversity of the microbiome, with an impoverishment of normally present, health associated, species and/or an enrichment of pathobionts (i.e., opportunistic pathogens present in low abundance in healthy microbial ecosystems but able to thrive in inflammatory conditions), disorders and diseases may occur. Dysbiosis may be featured by specific compositional and functional attributes in different disease contexts [21]. In many different diseases, however, the dysbiotic gut microbiome shows a reduction in the proportion of anaerobes that dominate the healthy gut and increased amount of facultative anaerobes, including Proteobacteria and Bacilli. It is interesting to note, but nobody should be surprised, that such low-diverse, disease-associated microbiome resemble the gut microbiome of perfectly healthy infants [22, 23]. This may be explained by the concept of "secondary succession" where a dramatic change that wipes out a complex community (such as a forest fire) results in the observation of similar early succession, or "pioneer" species. These phenomena suggest important reflections on the physiopathology of the gut microbiome, on which we are not going to dwell in detail in this chapter, but which are of great interest. One is that microbiome diversity is physiologically scarce in the child and, with different microbial actors, even in the elderly and that "special" compositions have been found in centenarians, thus hinting that their longevity may be consequent to "that" special composition of the microbiome, and not the opposite [24, 25]. Another topic of great interest is the study of the intertwining of environmental factors that throughout life lead some individuals to

contract a pathology, others another and some none. Let's think, for example, of the relationship between gut microbiome, host metabolism and immunity and diet in the determinism of colorectal cancer. It has been accepted for some time that the important role the gut microbiome plays in nutrient processing and synthesis may affect colorectal cancer development through metabolite-mediated changes in immune and metabolic signals [26]. Moreover, increasing data indicate that gut microbes are pivotal in integrating environmental cues with host physiology and metabolism and may influence several biologic processes critical to carcinogenesis including the balance of intestinal cell proliferation and death. For example, consistent data indicate that *Fusobacterium nucleatum* and *Bacteroides fragilis* are enriched in patients with colorectal cancer, whereas butyrate-producing bacteria are depleted in cancer patients [27]. Adherence to the Mediterranean diet is confirmed to have beneficial effects precisely because it leads to increased levels of fecal short-chain fatty acids (SCFAs) in relation to the presence of *Prevotella* and some fiber-degrading Firmicutes, which are fundamental to a healthy condition [28]. On the other hand, the long-term consumption of a low-fiber diet has been shown to have deleterious consequences on microbiota diversity and abundance profiles, which may be transferred over several generations, and not reversed simply by following a high-fiber diet [29].

Evidences have so far demonstrated that dysbiosis is the most relevant etiopathogenetic element for intestinal pathologies such as functional gastro intestinal disorders (FGIDs), in particular Irritable Bowel Syndrome (IBS), Small Intestine Bacterial Overgrowth, infections as *Clostridium difficile,* and Inflammatory Bowel Diseases (IBD). In these pathologies, it had long been suspected that the microbiota and its influences on the integrity of the intestinal epithelial barrier were somehow involved, while it has only recently become clear that dysbiosis is also involved in the pathogenesis of other frequent pathologies such as Celiac Disease, Diverticular Disease, and diabetes/sugar intolerance [30, 31]. Finally, based on multiple evidence it became clear that the old approach that placed intestinal functions (secretion, motility, immunomodulation, production of endocrine substances and others) under the control of CNS and ANS, i.e., the so-called brain–gut axis, should be completely overturned. At the origin of many diseases, or, one could say, at the base of the health status as a whole, there is a microbiome–gut–brain axis, to be intended as bidirectional interactions between the brain and the gut, with the microbiome as a third key player.

Preclinical and partly clinical evidence is increasingly convincing, indicating in the intestinal dysbiosis a relevant etiopathogenetic factor in neurodegenerative disorders such as Multiple Sclerosis [32] and Alzheimer [33, 34] and Parkinson's disease [35]. Incredibly, intestinal dysbiosis has also been reported in patients with neurodevelopmental disorders such as Autism [36, 37], Attention-Deficit Hyperactivity-Disorder [38], and Schizophrenia [39], and real psychiatric disorders such as anxiety and depression, and animal experiments strongly suggest that the correction of dysbiosis significantly affects symptoms and course of the disorder [40, 41]. Consistently, very recent studies have shown that the fecal microbiota transplantation improves the symptomatic picture in patients suffering from neuropsychiatric disorders [42].

11.4 Microbiome–Gut–Brain Axis

There are multiple ways, levels, and signaling mechanisms by which the microbiota can influence the interaction between the gut and the nervous system, including the brain. The components of this complex bond are a network of specialized targets/transducers cells in the gut wall functioning as an interface between microorganisms and the host lumen. This network consists of immune cells, enterochromaffin cells, smooth muscle cells, interstitial cells of Cajal, enteric neurons, epithelial cells, in particular dendritic cells [43]. In connection with external or internal disturbing factors, the brain acts by modulating the organization and functions of these cells via the branches of the ANS (i.e., through catecholamines and acetylcholine) and the hypothalamus–pituitary–adrenal axis (HPA). The microbiota is in constant bidirectional communication with this interface via multiple pathways, and these communication channels are modulated in response to perturbation of the microbiota, or the brain, by variations in the permeability of the intestinal epithelial barrier and the blood–brain barrier. In particular, to date, it is known that the intestinal microbiota can modulate the CNS through the following mechanisms: (a) synthesis of neuroactive microbial products (such as SCFAs); (b) stimulation of cytokine release by mucosal immune cells; (c) stimulation of the release of hormones (such as serotonin) by enteroendocrine cells, which enter the bloodstream and/or act on the surrounding nerves; and (d) direct stimulation of afferent fibers, such as the vagus nerve. Secondary bile acids and tryptophan metabolites are other microbiota-derived molecules with a role in influencing CNS neurotransmission but it is likely that many other mediators produced or contributed by the microbiota are able to cross the intestinal mucosa, enter the systemic circulation, and then cross the blood–brain barrier. Recently, a catalog of neuroactive potential of the human gut microbiome has been assembled, suggesting positive associations between butyrate producers (i.e., *Faecalibacterium* and *Coprococcus*) and higher quality-of-life indicators, probably mediated by SCFAs and the dopamine metabolite 3,4-dihydroxyphenylacetic acid [44]. However, it remains unclear whether the microbial-derived intermediates reach brain sites directly in sufficient local concentrations to modify distinct brain circuits, or whether microbial signals mainly communicate via neural pathways involving vagal and/or spinal afferents [45]. Brain–gut microbiome interactions are programmed during the first 3 years of life, including the prenatal period, but can be modulated throughout by diet and others factors as mentioned above.

11.5 Food and Microbiome–Gut–Brain Axis

With regard to diet, there is a fascinating relationship among food, immunity, and the microbiota. Diet is widely acknowledged as a pivotal determinant of the gut microbiota composition and function, capable of orchestrating the host–microbiome crosstalk, thus sustaining homeostasis or, on the contrary, contributing to disease susceptibility. Many dietary components are indeed known to interact with the microbiota, modulating the relative abundance of specific genera or the metabolite

landscape, with considerable ultimate effects on human health [46]. Though conflicting data are sometimes reported and more mechanistic work is called for, diet–microbiome–host research has great translational potential in the clinic, and it is likely that the interpretation of several diet-related signs and symptoms should be sought in the nexus with the gut microbiome. Foods, mainly plant-, fruit-, and animal-derived carbohydrates and proteins and fats, rapidly affect the composition and metabolic capacities of commensal microbiota. From an ecological point of view, altered environmental conditions exert selective pressure on various species, leading to competition for the most fit to survive and replicate. Through their enzymatic machinery, microbes convert dietary components into a series of molecules (e.g., SCFAs) that, once adsorbed, can reach the brain, so as to manipulate the host's eating behavior, generating cravings or dysphoria for certain nutrients. In addition, the microbiota can signal through structural components (i.e., microbe-associated molecular patterns—MAMPs) acting as ligands of Toll-like receptors, and inflammasomes, or NOD activators. From the host's perspective, the food supply is scarce and linked with geographic, seasonal, and ethnic parameters. Evolution has produced a highly optimized mutualistic system in which the maximum capacity of energy is extracted from a given amount of food while intestinal homeostasis is maintained. Consequently, animals have evolved mechanisms to modify the microbiota for their own benefit, such as via the mucus barrier and antimicrobial peptides (AMPs) [47]. It is worth remembering that the same quantities of ingested food can be processed differently, with a different number of extracted calories, depending on the individual-specific configuration of the microbiota and its metabolic capacities; in the case of dysbiosis related to persisting eating disorders, the resulting weight gain is then maintained in a self-sustaining vicious cycle. In other words, the substances produced by the gut microbiota for the same food ingested and therefore the signals that can cross the intestinal epithelial barrier and reach the brain can be profoundly different in different individuals, and result in distinct health outcomes [48]. Just think, for example, of the possibility that ingested carbohydrates are transformed into ethyl alcohol by an individual's microbiota and another not: absorbed alcohol may produce hepatic steatosis similar to that of drinkers, i.e., non-alcoholic hepatosteatosis, even in the absence of alcohol consumption [49]. Based on this increasing body of evidence, in the coming years we expect a growing number of studies on diet–microbiota interactions and health leading to the development of microbiome-targeted functional foods, with beneficial and even therapeutic effects for several disease conditions. Foods might one day be used in clinical medicine to prevent and treat diseases. The theory of "you are what you eat" finally is supported by scientific evidence.

11.6 Microbiome and Visceral Pain

Abdominal pain characterized by bloating and distention has been attributed to visceral hypersensitivity to mechanical and chemical stimuli. Many studies draw attention to a role of the gut microbiome in regulating intestinal sensation: they are mostly gnotobiotic studies showing transfer of the visceral hypersensitivity

phenotype after transplantation of gut microbiota from patients with FGIDs, generally IBS, into germ-free mice [50, 51]. Recent studies confirm that the gastrointestinal microbiota profile is altered in patients suffering from chronic or recurrent visceral pain [52, 53]. A correlation between visceral hypersensitivity and an increase of *Escherichia coli* abundance followed by induction of hypersensitivity in response to *E. coli* gavage in mice was found [54]. As this study and many others show, disruption of the gut microbiota in early life is associated with long-term changes in visceral sensitivity, emphasizing the importance of the gut microbiome in the neurodevelopment of pain pathways [55]. However, the exact mechanisms by which bacteria affect visceral perception and sensation still need to be determined, and it remains difficult to discern whether these changes are causative or deleterious to the host, or whether the altered microbiota signature is an appropriate response to tissue injury, inflammation, or damage in the host. Certainly, preclinical studies including prebiotic, probiotic, and antibiotic interventions, fecal transplantation, and the use of germ-free and specific-pathogen-free animals have illuminated our understanding of the role of the microbiota suggesting a few putative mechanisms. These include microbial induction of epithelial μ-opioid and cannabinoid receptors as shown after oral administration of *Lactobacillus* strains in rodents [56], regulation of central and peripheral neuronal pathways [57, 58], antinociceptive effects from inhibition of transient receptor potential vanilloid as shown with the administration of *Lactobacillus reuteri* in rats [59], microbial metabolites, particularly organic acids, or by-products such as nitric oxide altering sensation and affecting colonocyte cytoskeleton contraction and the subsequent tight junction opening [60], and microbial-derived bioactive molecules such as γ-aminobutyric acid (GABA) as shown with the administration of GABA-producing *Bifidobacterium dentium* [61]. There are others studies showing that probiotics blunt nociceptive response to colorectal distention [62, 63], but the translation of findings from animal models to human beings remains a challenge. For instance, rectal administration of butyrate has been found to increase colonic hypersensitivity in rats, but decrease visceral sensitivity in healthy subjects [64, 65]. In summary, the data suggest that intestinal dysbiosis, whether it is already present in the early stages of life and therefore affecting the development of pain pathways or whether it occurs later in life in relation to environmental factors, stress, diet, or others as mentioned above, may be the element that determines a low threshold of visceral pain, are very convincing. However, it will probably be very difficult to identify the substances produced or contributed by the intestinal microbiome, or microbiomes from other hollow organs in the pelvis, which are responsible for the onset and modulation of pain, as these can vary from individual to individual in relation to the resilience of their microbial ecosystem to short- and long-term perturbations in the host environment. Not least, the dynamics of the gut microbiome across the life span, with hallmark characteristics in the different phases of life, has to be accounted [66].

11.7 Microbiome and Colonic Motility

We have to consider a further mechanism trough which dysbiosis, particularly in the large bowel, can influence the onset of chronic recurrent visceral pain. Only recently, thanks to the works by the Australian group directed by the physiologist Marcello Costa, it has been possible to understand that propulsion in the large bowel is consequence of two neural mechanisms. The first is the content-independent spontaneous colonic migrating motor complexes that occurs cyclically. The second is a content-dependent, adaptable mechanism controlled by the mechanical activation of enteric neural activity. Mechanosensory enteric neurons (located in the myenteric plexus) have essential mechanosensitive nerve endings in the circular muscle. Distension or stretch of the colon activates these sensory neurons to initiate polarized neural pathways that result in oral contraction and anal relaxation. These pathways do not require the mucosa but can be modulated by sensory nerve endings that project into the mucosa [67]. Enteric neural circuity can efficiently propel content with a wide range of physical properties. This content-dependent activity can be modified in terms of force of contraction and speed of propulsion depending upon consistency and volume of the colonic contents [68]. In others words, bolus size and its consistency affects propulsion speed suggesting that propulsion is not a simple reflex, according to the classic theory about intestinal peristalsis [69], but rather a more complex process involving an adaptable neuromechanical loop [70]. Consistency depends on the degree of fluidity of the intraluminal colonic contents, which in turn depends on the degree of absorption of fluids along the colon. But consistency is due also to the dry-component of the formed stools, and this is for the 60-80% composed by alive microbial cells originating from the colon microbiota [71]. So, when a relevant impoverishment of the microbial biomass occurs in the large bowel, that significantly influences colonic propulsion capacity. The resulting decrease in transport of the intraluminal contents can generate dysmotility phenomena with the onset of spasticity in some colonic tracts and distension/dilatation in others. It is well known as both these conditions cause visceral pain, particularly in individuals having a decreased threshold as a consequence of dysbiosis and changes in the microbiome–gut–brain axis as discussed above. It can be said that an empty colon has no motor activity and this is very important for explaining many cases of constipation where disturbances of defecation were consequence of profound imbalance in diet habit, antibiotic consumption. It should be noted that for fibers and prebiotics the mechanism of action is not due to a "mass" effect resulting from a recall of water produced by the polysaccharide molecules of which they are made up, but their action, which favors evacuation, derives from the fact that they constitute the main metabolic substrate for the colon microbiota, and that, as we have seen, the biomass constitutes the dry weight of the feces [72]. It follows that the primary objective of every therapy for constipation is certainly to achieve defecation but not "di per sè," but as a way of rebalancing the ecosystem in the intestinal lumen [73]. In our study, we demonstrated that in a population of patients with severe functional constipation it was enough to restore a regular colonic content

using a symbiotic product for improving defecation disturbances [74]. Finally, colonic dysmotility and so visceral pain due to spastic and dilatation aspects in the large bowel may be the direct consequence of dysbiosis, independently by change in the intraluminal content volume, because function and neuroplasticity of the enteric nervous system are influenced directly by intestine metabolome: butyrate may affect neurochemical coding of myenteric neurons and the contractile activity in the rat colon upon long-term exposure. We can speculate that reduced concentration of butyrate in the gut lumen, inducing alterations in cholinergic neurons of myenteric plexus, is only an example among many how colonic motility can be influenced by microbiome imbalance [75].

11.8 Perspective

There is no doubt that the administration of specific probiotic strains, for which, as for antibiotics, a precise target and therefore a clear therapeutic indication have been identified, is the right means to correct dysbiosis and restore balance in the intestinal ecosystem, thus affecting the threshold of appearance of visceral pain. In this regard, it is worth mentioning the success of probiotics, such as *Lactobacillus reuteri* and *Lactobacillus rhamnosus*, and the synbiotic combination of Fructo-Oligo-Saccharide and seven probiotics in treating the infant colic: two meta-analyses including more than 400 infants found that *L. reuteri* significantly reduced crying time in formula-fed infants by nearly 1 h a day, making it the most extensively studied microbiome-targeting therapy for colic [76–79]. Future treatment strategies for the alleviation of chronic or intermittent visceral pain should take into consideration the personalized microbiota alterations by identifying subsets of patient with a distinct microbiota profile, and developing targeted approaches to restore specific populations of beneficial bacteria. In this regard, the fecal microbiota transplantation (FMT) deserves a separate discussion. We have seen that the human gut microbiota is not a mere assembly of microorganisms, but a highly organized integrated network of cells interacting intensely with each other as well as with the host, which could be thought of as an additional organ within the human body. Based on the available literature, the possibility of transferring this "organ" from a healthy individual, i.e., endowed with a high-diverse intestinal microbiota, to an individual whose microbiota is impoverished, unbalanced, and unable to oppose the action of pathogens has proved to be highly effective and statements on FMT indications, donor selection, preparation of fecal material, clinical management and fecal delivery, and basic requirements for implementing an FMT center are already well established [80]. The first and most documented clinical application of FMT is recurrent *Clostridium difficile* infections (rCDI) in which it is currently used as a last-resort treatment after failure of multiple courses of antibiotics [81], but beyond rCDI, FMT has been evaluated as a treatment option in a variety of gastrointestinal diseases, such as Inflammatory Bowel Diseases [82, 83], non-alcoholic steatohepatitis, alcoholic hepatitis, and hepatic encephalopathy [84, 85]. The evidence that FMT

can be useful in the treatment of disorders as IBS [86] and constipation [87] is very interesting, confirming what we have discussed, i.e., in this disorder intestinal dysbiosis and altered interaction with gut mucosa are pivotal. Moreover, extremely interesting it is that manipulation of gut microbiota through FMT seems to be effective also in conditions outside the GI tract, such as Autism and mood disorders [88] and the Metabolic Syndrome [89]. It is intriguing to speculate that FMT could prove to be an interesting approach for the treatment of patients with severe CPP, when all other therapeutic options have failed, precisely for these its effect, both on the intestinal mechanisms of visceral pain and of influencing the brain functions and mood stability. In fact, it is well known that problems of anxiety, depression, sexual abuse, psychiatric disorders, and often personality disorders are overrepresented in the population of patients with CPP. Studies about this possibility are very desirable, and they can take advantage of a longitudinal systems-based disease model with complementary brain imaging in order to integrate central, peripheral, and behavioral alterations before, during, and after treatment [90].

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The Role of the Pelvic Floor: Does Overactivity Count in CPPS?

12

Antonella Biroli

The Pelvic Floor Clinical Assessment Group of the International Continence Society (ICS) in 2005 stated that "Non-relaxing pelvic floor means that there is no palpable voluntary or involuntary relaxation of the pelvic floor muscles (PFM)" considering that involuntary relaxation should occur, i.e., when straining as if defecating. When bringing attention to symptoms and signs, pelvic floor muscles overactivity is defined as "a situation in which the PFM do not relax or may even contract when relaxation is functionally needed, for example during micturition or defecation. This condition is based on symptoms as voiding problems, obstructed defecation or dyspareunia and on signs as the absence of voluntary PFM relaxation" [1].

PFMs overactivity in the last decades has been brought into play in a long list of different pelvic dysfunctions, as dysfunctional voiding, functional defecation disorders, sexual problems as vaginismus and dyspareunia, and also in chronic pelvic pain syndrome.

12.1 Pelvic Floor and Chronic Pelvic Pain: The Relationship

The European Association of Urology (EAU) Guideline on Chronic Pelvic Pain (CPP) bases on an 8-Axis Classification. The Axis I (Region) identifies the pelvic region, the Axis II the involved system (Urological, Gynecological, Gastrointestinal, Peripheral nerve, Sexological, Psychological, Muscle-skeletal), while the III Axis is focused on the end organ [2]. Pelvic floor is considered one of the end organs, that is to say that pain can be localized specifically in this muscle group. End organs are the sites where patients refer pain, not being necessarily the "guilty" organ that causes pain. "Pelvic floor muscle pain syndrome" occurs when the persistent or

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recurrent pain site is identified in this region and the syndrome "may be associated with overactivity of or trigger points within the PFM or other several muscles" [2].

Nevertheless the role of the PFM, as well as that of the central nervous system, is probably transversal in chronic pelvic pain syndromes (CPPS), being not limited to the definition of specific pain in this area. Indeed the nervous system has shown to be strongly implicated in the pathogenesis of chronic pain. The central sensitization phenomenon implies an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity [3], exiting in dysfunctional pain syndromes. Both central pain generators and peripheral pain generators can contribute in maintaining CPP, including bladder pain syndrome/interstitial cystitis (BPS/IC), vulvodynia, and myofascial pelvic floor pain [4]. As well as nervous system, pelvic floor muscles have been involved in CPPS pathogenesis. The convergence and summation of visceral and somatic afferences at spinal and supraspinal level are responsible for the double role that pelvic floor muscles may play in chronic pain. Increased and abnormal visceral afferents have shown to increase tone in correspondent regional skeletal muscles by activating alpha and gamma motoneurons through a viscero-somatic reflex, a phenomenon well-known for example in appendicitis, when abdominal rigidity, due to muscle stiffness and abdominal antalgic guarding reflex are common signs. Analogously, pelvic visceral pain and inflammation may cause pain in somatic structures innervated by the same spinal segment by viscero-somatic convergence, exiting in PFM pain and dysfunctions. On the other side, pelvic floor altered function may contribute to pelvic dysfunctions, i.e., voiding, defecation, sexual, postural dysfunctions, finally resulting in a cascade of reactions involving the central nervous system.

Pelvic viscera and muscles of the pelvic area are strictly connected to each other. Contiguity implies sharing the connective fascial pelvic system and also the pelvic space, where abdominopelvic pressure changes accordingly with different postures and muscular (diaphragmatic, abdominal, and PFM) activity. Bladder, bowel, and sexual functions depend on fine coordination between autonomic and somatic system, being PFM an important factor in this complex mechanism. Moreover, visceral and somatic afferences converge in spinal cord, as previously described, and these two systems affect each other.

Consequently, PFM is probably involved in a vicious cycle of cause and consequence together with the central nervous system and its plasticity, representing part of the pathogenetic mechanism in different types of chronic pelvic pain syndromes, also when PF is not specifically the end organ.

This hypothesis finds some support in two different branches of research, one oriented to study the association between PFM myofascial pain and chronic pelvic pain, the other the effectiveness of myofascial PFM treatment on chronic pelvic pain.

When considering the first branch, pelvic muscle tenderness was found in 58.3% of CPPS affected women and in 4.2% of controls [5]. Tu reported levator ani and piriformis muscle tenderness in 22% and 14%, respectively, of 987 CPP women [6]. In a population of women with interstitial cystitis (IC) and pelvic pain Peters found that 87% complained of pelvic floor pain at palpation [7]. Increased prevalence of

pelvic floor "spasm" (but not of PFM trigger points) was found also in subjects diagnosed with deep endometriosis (53.9%) compared to controls (17.3%) [8]. Morin demonstrated greater resting forces and stiffness measured by dynamometry and greater muscle activation during stretching by EMG in women with provoked vestibulodynia compared to controls [9].

Also when considering male populations, increased pelvic floor muscles tone and tenderness were demonstrated in CPP affected versus healthy men [10]. Shoskes found that 51% of CPP men show tenderness vs. 7% of controls, being the most common site the prostate (41% CPPS, 5% controls), followed by external and internal pelvic floor (13% and 14% CPPS, 0 controls) and suprapubic area (9% CPPS, 0 controls) [11].

Searching more objective evidences, Lenore Ackerman studied a small population of patients with IC/BPS and controls using MRI, concluding that patients with IC/BPS have pelvic floor hypertonicity, demonstrated by shorter levator muscles, wider posterior pubo-rectalis angle, and decreased puborectal distances [12]. Morin showed that, at rest, women with provoked vestibulodynia had larger levator plate angle, more acute anorectal angle, and smaller levator hiatal dimension at ultrasounds compared with controls, due to a higher PFM tone [13].

So, increased PFM tone and tenderness seem to be more prevalent in CPPS population compared to controls. On the other side, a second branch of research showed that treating pelvic floor trigger points and relaxing muscles result in CPP symptoms and quality of life improvement.

As early as 1963 Thiele reported cure in 68% of subject affected by levator ani spasm, using transrectal massage. In the next decades, a certain number of studies focalized CPP treatment on pelvic floor [14]. Langford applied anesthetic infiltrations in pelvic floor trigger points in 18 CPP women, showing pain reduction, evaluated by visual analogic scale [15]. Bartley also demonstrated decrease in pain levels after pelvic floor trigger point anesthetic injections [16]. Oyama found that PFM massage was useful for 21 women with IC and PFM increased tonus [17]. Bertolasi treated women with vaginismus by EMG guided botulinum toxin infiltrations [18], analogously Abbott successfully treated pelvic floor spasm associated to dyspareunia and pelvic pain [19]. In 2005, Cornel used an association of biofeedback and manual therapy in men with chronic prostatitis/prostate pain syndrome (CP/PPS) demonstrating an amelioration in Chronic Prostatitis Symptom Index [20]. In a RCT, Fitzgerald treated 81 women with IC/BPS showing improvement in 59% of women having manual pelvic floor physical treatment compared to 26% having a global massage treatment [21]. Weiss referred improvement in 83% of patients with IC and urethral syndrome treating PFM trigger points [22]. Glazer treated a group of 62 women with vulvodynia by surface EMG assisted biofeedback pelvic floor rehabilitation, and 88% reported no pain after treatment [23]. Anderson obtained a reduction in number of patients using medication from 63% at baseline to 40% after following for 6 months a protocol of pelvic floor myofascial trigger point release associated to paradoxical relaxation therapy in 374 patients with refractory CPPS [24].

Despite very low-quality level of evidence and the consequent uncertainty about the real effects of conservative therapy involving pelvic floor treatment, as pointed out in a recent Cochrane review for chronic prostatitis/CPPS [25], a certain number of studies has been conducted in this field that keeps the scientific world interested. Obviously pelvic floor treatment represents only a part of pelvic pain management, assuming more importance when specifically a pelvic floor muscle pain syndrome is diagnosed. EAU guidelines conclusions about pelvic floor treatment report that the use of biofeedback (BFB) is the preferred treatment for chronic anal pain syndrome (strongly recommended); PFM therapy can be part of the treatment in sexological aspects of CPP; and finally that myofascial treatment is effective (grade 1b evidence, weak recommendation) as first-line therapy, eventually adding Biofeedback as adjuvant to muscle exercises (strong recommendations) in case of pelvic floor dysfunction [2].

It is now clear that CPPS is a variegated group of syndromes, so in the last decade we are assisting to an effort to further differentiate them, in order to provide more type-oriented and individualized, though always multimodal, therapies. This approach, based on clinically relevant phenotypes, could provide a rational guide to treatment.

One more time, the pelvic floor muscles play a relevant role, being one of the element for phenotyping CPPS. For example, when looking at provoked vulvodynia, in 2009 Goldstein proposed a classification: hormonally mediated subtype, congenital and acquired neuroproliferative subtype, and pelvic floor muscles dysfunction associated subtype [26]. In more recent years, Henzell tried to differentiate provoked Vulvodynia into four subtypes, depending on predominance of overactive pelvic floor, peripheral inflammatory mechanisms, emotional and psycho-social factors, or the presence of pain comorbidities [27]. When considering urological pain, the U-point system is meant to classify individuals with CP/CPPS and IC. It is based on a 6-domains evaluation: Urinary, Psychosocial, Organ specific, Infection, Neurologic system, Tenderness of skeletal muscles (giving birth to the acronym U-POINT). So, tenderness suprapubic or tenderness, spasm or trigger points in pelvic floor muscles are specifically investigated and contribute to characterize individuals with urological CPPS [28].

The growing interest in pelvic floor muscle function and chronic pelvic pain syndromes involves other structures, as PFM should not be regarded as an isolated system. Trigger points, increased tone, and dysfunctions can be found also in obturator internus and abdominal muscles and their insertions, as in glutei, psoas, and piriformis muscle. Moreover, the muscular system is strictly connected with the articular system: sacroiliac joints, pubic symphysis, sacrococcygeal and coccygeal joint, and, finally, hips dysfunction can be involved both as cause and consequence of pelvic pain.

Looking to musculoskeletal abnormalities other than pelvic floor ones, chronic pelvic pain patients showed in a study to have a higher prevalence of more asymmetric iliac crests, pubic symphysis heights, tenderness of abdominal muscles, and less ability to maintain PF relaxed compared to controls [29]. Montenegro found abdominal myofascial pain in 15% of CPP affected women [30] and even more cervical spine postural changes and winged scapulae in a group of 108 CPP compared to controls [31].

Postural changes can be both cause and consequence of persisting pain. Indeed, lumbopelvic posture and dynamics can be influenced by many factors. For example, in pregnant women, when the growth of uterus makes necessary that abdominopelvic cavity expands and compensates the increasing abdominal pressure, postural changes often result in lumbar hyperlordosis and anterior pelvic tilt, an "anterior opened posture." On the contrary, in occasion of abdomino-pelvic pain, a posterior pelvic tilt, abdominal contraction, and hypolordosis could represent a sort of "protective posture."

Indeed, when examining a patient with CPPS, the pelvic floor assessment should be intended with a more extended approach. In 2019, Meister proposed a screening (before that diagnostic) examination protocol for assessment of pelvic floor myofascial pain, starting with sacroiliac joints, pubic symphysis, obturator internus (OI), and levator ani examination, palpating the center of PF muscle belly and then all along its length [32]. A detailed description of physical examination in CPP is also part of the SOGC Consensus Guidelines for the management of chronic pelvic pain: it points the attention on hip and pelvic region joints function and symmetry, and on tenderness and trigger points research in abdominal, adductor, lumbar paraspinal, quadratus lumborum, gluteus maximus, medius and minimus, piriformis, obturatoris internus, and, finally, levator ani muscles [33].

12.2 Pelvic Floor Muscles: The Physiological Basis of Muscle Tone

In CPPS affected population PF muscles are often reported to be contracted at rest or "hypertonic," making it necessary to deepen the concept of tone. "Muscle tone" can be defined as the resistance provided by a muscle at rest when stretching is applied. Commonly it is also defined as the minimal muscle contraction (or better, the overall muscle stiffness) at rest in a balanced state. From a broader perspective, tone can also be seen as the "preparing state" of muscles to specific functional tasks, a definition that points out a more dynamic concept of tone.

A basal reflex tone, under nervous system control, is considered part of the postural control, but in the last two decades there is an ingrowing interest in a component not related to CNS control and EMG-silent [34]. When the individual is in an equilibrated gravity neutral posture in a fully relaxed condition, also in absence of EMG activity, there is an intrinsic tension defined HMRT (human resting muscle tone), that is of small amount, about 1% maximal voluntary contraction [35]. So two components of tone can be distinguished: a passive resting intrinsic tension that is silent at electromyography, due to an elastic and a viscoelastic component, and an active tone, activated or controlled by the central nervous system. The passive tone contribution to balanced posture could represent an energy saving efficient mechanism, whereas unnecessary muscle contractions at rest could be the result of interfering factors, as anxiety or bad habits.

On the other side, the active tone regulation depends on both peripheric and central components. The neuromuscular spindles (situated in the muscle) and the Golgi's organs (in the tendons) are part of the peripheric system. Type Ia nervous

fibers provide sensory innervations, while gamma fibers provide motor innervation to neuromuscular spindles. They are the physiologic basis for myotatic excitatory reflexes (as the patellar reflex) and for inverse myotatic reflex (responsible for antagonist inhibition). Type Ia fibers have excitatory connections with Ia motor neurons, so, when muscles are stretched or spindle fibers contract, the muscle is activated and antagonist muscles are inhibited. The final scope is to maintain a constant tone in the body by a reflex mechanism. On the contrary, Golgi's organs, innervated by sensory Ib fibers, when stimulated, have an inhibitory effect on alpha motor neurons responsible for muscle contraction. This inhibition acts as a protective mechanism avoiding muscle overloading [36].

Interestingly, while the periurethral levator ani normally is provided with muscle spindles, they are absent in the external urethral sphincter, suggesting that the tone of this particular muscle is regulated by different and specific reflex arches [37].

The central regulation of active tone depends on descending tracts, as corticospinal, rubrospinal, and dorsal reticulospinal tract, responsible for control on flexor muscles, and vestibulospinal and medial reticulospinal tract, for extensor muscles [36]. It is well known that the loss of the inhibitory descending control, due to neurological diseases, causes hypertonus, spasticity, and dystonia, as occurs after stroke or spinal lesions. Moreover, hyperreflexia and hypertonus can be also found in stressing conditions, as result of an alert state [38]. When muscle tone is increased in neurological disease, the term "hypertonus" is commonly used, whereas it could be better to use the definition "increased tone" in all the other cases [39].

At rest, in balanced state, it is possible that no EMG activity is found, but in some muscles, mainly with a postural function, an active neurogenic activity is often EMG detectable. This activity increases during mental tasks or excitation and is reduced by relaxation. The role of the active components of tone varies depending on muscles, individuals, conditions, in different studies. It is not clear the reason why the tone of pelvic floor muscles is increased in some subjects, but it is conceivable that more than one factor is involved: lifestyles, unfavorable patterns of movement, asymmetric posture, previous surgical or obstetric trauma, and visceral pain. Anxiety and stress are often accompanied by increased muscle tone, and pelvic floor tone could be part of a more general response. Moreover, the role that pelvic floor plays in fundamental and intimate functions as the urological, sexual, and defecatory ones could also imply its increased activation with the aim to "protect" the important crossroad of visceral systems represented by the pelvic region.

12.3 Pelvic Floor Muscle Overactivity: What Can We Observe?

12.3.1 How to Measure the PFM Tone

Tone is commonly evaluated by digital palpation in routine clinical practice, but unfortunately it is a subjective method. Other techniques have been proposed, nevertheless everyone presents with advantages and problems. Manometry can be used to estimate vaginal or anal resting pressure, which in part depends on pelvic floor

muscle tone. Surface electromyography amplitude at rest provides a useful measure, but it did not show a very good reliability [40]. Moreover, it measures only the active component of tone. The use of a dynamometry can be added to EMG techniques in order to investigate both active and passive components of tone [41]. Indeed, to differentiate the contribution of active and passive components in increasing muscle tone could be very important to address a more oriented treatment. In fact, the increase in active tone could benefit of relaxing manual and biofeedback techniques, while the passive tone should be treated by manual or other stretching techniques. Finally, imaging techniques as ultrasound or MRI provide data about morphology and dynamics of pelvic floor and linked structures, as levator hiatus dimensions, anorectal angle, and coccyx position that are indirect indicators of PFM tone.

12.3.2 Beyond the Concept of Tone

Overactivity and pelvic floor dysfunction in chronic pelvic pain are not synonymous with increased muscle tone. In literature, the signs associated to CPPS are variously reported as pelvic floor muscles tenderness, spasm, increased tone, increased stiffness, abnormal EMG activation during stretching, shorter muscles, and finally trigger points.

Simons and Mense in 1997 tried to make the factors contributing to muscle tension more defined. According to this work, contracture is a state of contractile activity within the muscle in absence of detectable EMG activity, although this term is often also used for muscle shortening, due to a prolonged shortened position [42]. In this second case modifications of the connective tissue intervene and the muscle is retracted. On the contrary, muscle spasm is EMG activity not related to posture and not under voluntary control [42]. Cramps are a form of painful muscle spasm.

In 2016, the International Continence Society published a report aimed at the standardization of terminology in chronic pelvic pain syndromes. The musculoskeletal signs associated to CPPS were examined, offering a summary of definitions for concepts as muscle tone and its disorders, stiffness, compliance, tension, spasm, contracture, trigger, and tender points [39].

Pelvic floor dysfunction in CPPS is often described as myofascial pain syndrome, a condition characterized by pain in presence of trigger points. The diagnostic criteria for trigger points are the presence of a tender nodule in a palpable taut band that, when palpated, reproduces the usual pain in the patient. A sustained contracture in the skeletal muscle can be found, restricting range of motions and a local twitch response when the TP is palpated is called the jump sign [43]. Interestingly, the taut bands at rest are EMG silent, suggesting that trigger points and surrounding contracture are local manifestations, not CNS mediated [41]. Myofascial trigger points are distinguished in active (when producing local or referred pain or sensory disturbances), or latent, asymptomatic unless activated by a stressor. Tender points can also be found and are more generally points of tenderness at palpation, that not necessarily meet all the requirements to be considered trigger points. Trigger points

can be found in the muscles and also in the connective tissues as fascia. Compression or stretching of the interested muscle often provokes pain. Mechanical factors, such as postural alterations or abnormal patterns of movement or trauma can be the cause of muscular strain and overload, provoking pain and giving birth to trigger points.

Pelvic floor muscles in CPPS often show abnormal pattern of movement. An abnormal protective reflex is responsible for dysfunctions as vaginismus, or anismus, characterized by a various grade of pelvic floor contraction response in occasion of sexual intercourse, or during medical examination. Also when the uro-procto-genital area is not painfully interested by stimuli, an abnormal and exaggerated pelvic floor activity can be seen as a part of an individual pattern of movement, establishing longtime contractures and retractions. The normal PFM relaxation required for defecation or micturition can be absent or substituted by contraction, exiting in disorders as dyssynergic defecation or lower urinary tract dysfunctions, i.e., dysfunctional micturition.

It is worthwhile to note that pelvic floor is not an isolated entity, so when speaking about its dysfunction it should be remembered that PFM behavior depends on a network, involving other muscle and structures. For example, pelvic floor is an important factor in the straining movement, as it should relax, but it is all the complex of the "piston" action of the diaphragm, "holding" action of abdominal wall (transverse and oblique muscles) and of the more lateral component of pelvic floor, that makes the final scope achieved. If straining is not correctly oriented towards the anus, also if pelvic floor does not dyssynergically contract, it could be difficult to obtain the normal stretching effect added to relaxation of pelvic floor that matches a functional straining.

Finally, pelvic floor is not considerable only as a single global entity, as the muscles that constitute it are primarily the levator ani, made up by more than one component, but also other important structures, as the anal and urethral striated sphincter, the bulbocavernosus and ischiocavernosus muscles. So it is possible to find trigger and tender points and contractures in different muscular and tendinous sites. An interesting line of research aims to recognize different PF muscles behavior depending of the aim of the movement, going beyond the concept of an only massive movement of pelvic floor. Dysfunctional voiding represents an interesting example in this field of research where authors tried to differentiate the behavior or prevalence of a muscle compared to others. Dysfunctional voiding is characterized by an intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated or levator muscles during voiding in neurologically normal individuals. Some Authors tried to distinguish the contribution of the striated external urethral sphincter or the pelvic floor (levator ani) muscle to abnormal micturition. Deindl used kinesiological EMG for measuring pubococcygeal activity, needle EMG for external striated sphincter muscle and urodynamics in 15 patients affected by dysfunctional voiding /urinary retention: inappropriate pelvic floor activation during voiding was detectable in 11 pts., urethral sphincter activation in four patients, showing a positive response to biofeedback training in the first group, but not in the second group [44]. In an other study women with symptoms and signs of bladder outlet obstruction showed at videourodynamics bladder neck

obstruction in 8.7%, urethral sphincter obstruction in 27.1%, pelvic floor muscle obstruction in 51.2%, being the criterion for urethral sphincter obstruction a narrowing at the mid-urethra at voiding cystourethrography, while the criterion for pelvic floor muscle obstruction was when the narrowing site was at the distal urethra, where the pelvic floor muscles surround it [45]. Although these are not commonly recognized criteria and more studies are needed to deepen the theme, the idea to consider the pelvic floor recruiting more than a unique movement is interesting and important in order to provide more tailored treatments to patients affected by pelvic floor dysfunctions.

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How Pain Influences Sexuality in Men

13

Manuela Tutolo and Andrea Salonia

13.1 Introduction

Knowledge of normal male sexual function and the causes of sexual dysfunction have become better understood, and more effective treatments are available. However the majority of the studies are small, short-term follow-up, case series, mainly focusing on hormonal, neurologic, psychologic and/or vascular issues [1]. Moreover, there is a lack in the field of sexual medicine research on the biologic contribution of pelvic floor disorders to different male sexual dysfunctions.

Male sexual dysfunctions include:

- Erectile dysfunction (ED)
- Diminished libido
- Abnormal ejaculation

Abnormal ejaculation includes a plethora of heterogeneous disorders, namely: premature, delayed, and retrograde ejaculation, anorgasmia and painful orgasm or male dyspareunia.

Male dyspareunia is defined as recurrent or persistent genital or pelvic pain with sexual activity or sexual dysfunction that is present for 6 months or longer, often in the absence of organic aetiology [2].

Men with pain during sexual activity represent a real challenge for practitioners because of the lack of a uniformly accepted classification and because, in the majority of cases, the aetiology of this disorder is multifactorial and includes psychological and biological issues.

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As a matter of fact, pain during sexual intercourse can represent a common symptom of different pelvic floor dysfunctions. Pelvic floor is a complex system of muscles, fascia, ligaments, bone, nerves and vascular supply; this complex system plays a crucial role in urinary, bowel and sexual function [1]. Multiple factors including nerve injury, inflammation, peripheral hyperalgesia, metabolic disorders and other pathological conditions may dramatically affect the function of an adjacent visceral organ due to viscerovisceral cross-sensitization. Coordination of reflexes and normal functioning of the urinary bladder, colon and reproductive organs are controlled not only by complex mechanisms in the spinal cord, but also involves supraspinal neural pathways. Axons of neurons in the spinal cord receiving afferent inputs from the pelvis project to the brainstem, hypothalamus and, through relay neurons, to the cortex [3]. Descending pain pathways appear to be important components in the development of visceral hyperalgesia in the pelvic area. This should be taken into account when facing with patients with pelvic floor disorders, where an organ-oriented approach can lead to a misleading diagnosis and subsequent management.

To clarify symptoms, signs and further evaluation of pelvic pain in general, the ICS working group standardized the terminology of pelvic pain in nine different domains in order to improve diagnosis and management of these disorders. In particular, the VIII domain includes sexual pain disorders that occur during sexual intercourse and can be referred to the penis, perineum or occur during ejaculation. This can lead to lack of desire, arousal, orgasm, ED and consequently to depression and relationship issues [4].

13.2 Epidemiology

Approximately 1–5% of men suffer from dyspareunia defined by patients as a painful and uncomfortable feeling during sexual intercourse [2, 5]. However it should be noticed that the low reported incidence can represent either the real uncommon occurrence of this condition or the lack of disclosure because it represents a real stigma leading to an underreported incidence in the majority of the series.

13.3 Aetiology and Symptoms

In general, male dyspareunia can be divided into four broad categories based on the suspected underlying aetiology [2]:

- Isolated ejaculatory pain
- Chronic prostatitis/chronic pelvic pain syndrome
- Medical causes
- Other causes

Isolated Ejaculatory Pain: This is a sub-type of ejaculatory dysfunction and can be idiopathic or caused by identifiable dysfunctions. Its incidence varies between 2% and 7% in men aged more than 50 and it increases when lower urinary tract symptoms (LUTS) are present. The aetiology of isolated ejaculatory pain is multifactorial and can have inflammatory, malignant, benign, surgical, iatrogenic or psychiatric origin. Sometimes it derives from ejaculatory duct obstruction [6]. Typically, pain is suprapubic, at the level of the penis, but can also occur in the lower abdomen, urethral meatus, testis and less likely at the level of the rectum [7].

Among surgical aetiology one that is worth of consideration is radical prostatectomy (RP). Indeed, data from open RP (ORP) series have shown impairments in sexual desire, orgasmic function and penile morphology after surgery. Among these conditions a non-negligible incidence of climacturia, ejaculatory pain and impaired orgasmic sensation have been reported [8–10]. Previous data have reported up to 19% of patients complaining of painful orgasm after RP [10]. A postulated theory regarding the occurrence of a muscle spasm or dystonia in the bladder neck and/or pelvic floor at the time of orgasm has been considered as the main explanation for reported post-RP painful orgasm [11] (Fig. 13.1).

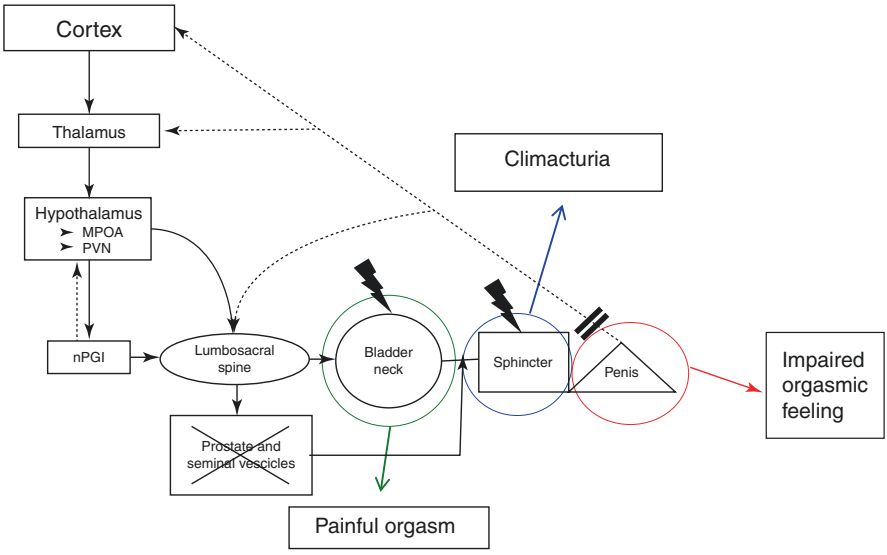

Fig. 13.1 Orgasmic alterations after radical prostatectomy [with permission from P. Capogrosso et al.] [10]

13.3.1 Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CPPS)

Defined as persistent or recurrent episodic chronic pelvic pain for at least three of the preceding 6 months in the absence of other identifiable causes. Non-infectious aetiology (trauma, autoimmunity, neurogenic pain, increased prostate volume, somatic and psychologic factors) have been proposed but none has been proven.

In the majority of cases no proven infection or other obvious local pathology are found.

It is of notice that LUTS and pelvic pain due to pathologies of the prostate have always considerably affected quality of life of men of all ages [12, 13].

Sexual dysfunctions associated with CP/CPPS are not uncommon. Prevalence rates of erectile dysfunction in these men have been reported to range between 40% and 72% (difficulty with either erections or ejaculation). As a result of the pain, Aubin et al. showed that 70% of men with CPPS reported a decrease in their sexual desire, 40% increased problems with sexual function, and 29% with masturbation. Moreover, 13.5% reported having pain at ejaculation most of the time or always [14].

13.3.2 Medical Causes

Several medical causes of male dyspareunia have been described. However, data often come from small case series, low-quality studies:

- Peyronie disease (PD): acquired, localized fibrotic disorder of the tunica albuginea resulting in penile deformity, mass, pain and, in some men, erectile dysfunction. The prevalence of PD is approximately 5% in men [15].
- It can represent a psychologically and physically disabling disorder, leading to a lower quality of life. An insult (repetitive microvascular injury or trauma) to the tunica albuginea is the most widely accepted hypothesis on the aetiology. A prolonged inflammatory response will result in the remodelling of connective tissue into a fibrotic plaque [16].
- Frenulum breve: causing restriction of the glans during erection.
- Phimosis: abnormal restriction of the opening of the foreskin.
- Herniorrhaphy sequelae and pudendal nerve entrapment: mainly due to intervention along the course of genitofemoral, ileoinguinal and pudendal nerves. This pain has been reported in almost 3% of men following inguinal hernia repair [12].
- Ejaculatory duct obstruction: due to cyst of calculi.
- Genito-urinary infections.
- Chronic bladder pain: in this case, compression of the bladder during intercourses can cause an intense pain that can completely inhibit intercourse.
- Dermatologic conditions.

Other Causes: psychological traumas (history of abuse, body image issues, relationship difficulties) or medications can considerably influence sexual intercourses that can be perceived as a painful experience.

Regardless of its different possible aetiology, male dyspareunia is associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction [12].

13.4 Diagnosis and Management

Regardless of the underlying aetiology, the majority of the conditions associated with male dyspareunia can be disclosed with an accurate anamnesis, symptom assessment and physical examination. Further investigations are usually not necessary.

In particular, it is necessary to meticulously focus on sexual history, habits, presence of other urinary symptoms, psychological status, medications or previous traumas. Physical examination should focus on genital area with attention on penis, prostate, sphincters and pelvic floor muscles tone.

Laboratory studies should be performed in case of dysuria or other urinary symptoms.

The management of male dyspareunia, if possible, should be directed to its underlying cause.

It is of notice that, in the majority of cases, due to the multifactorial origin of this condition and overlapping symptoms that can be common in different pelvic floor dysfunctions, a clear underlying aetiology is hard to find. Therefore, this condition is, quite often, poorly managed.

The management of male dyspareunia requires a multimodal, symptomatic approach, knowledge of all pelvic organ systems and their association with other systems and conditions, including musculoskeletal, neurologic, urologic and psychological aspects, promoting a multidisciplinary approach.

The presence of pain associated with sexual intercourse has been linked to reduced quality of life and negative interpersonal relationships. This is of outmost importance when facing with this group of patients. If the clinician identifies psychological basis for male dyspareunia or an extremely negative impact of this condition on personal and social behaviours, a sexual counselling specialist is recommended [2].

In general, a multimodal approach to the underlying cause is recommended whenever possible.

European guidelines advocate a bio-psychological management as the management of choice for this condition with an active involvement of the patient. Single interventions rarely work in isolation. Pharmacologic and non-pharmacologic 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 [12].

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Overactive Bladder and Chronic Pelvic Pain Syndrome

14

Matteo Balzarro

14.1 Introduction

The overactive bladder (OAB) is a symptom syndrome defined by the presence of urgency, with or without urge incontinence, but usually with frequency and nocturia in the absence of infection or other obvious etiology [1]. Other pathologies like a urinary tract infection, bladder stones, and oncological conditions should be ruled out. In this syndrome urgency is the pivotal symptom. This is a sensation that makes you to go to the bathroom immediately (= urgency), and often (= frequency) to urinate. In case you have to wake up to do that at night it is called nocturia, and in case you do not get in time to the toilet with involuntary loose urine (= urinary incontinence) it is called wet-OAB. Blaivas noted that "Urgency is comprised of at least two different sensations. One is an intensification of the normal urge to void and the other is a different sensation. The implication of this distinction are important insofar as they may have different etiologies and respond differently to treatment" [2]. Although the introduction of the definition of OAB has been widely accepted, it should be emphasized that for some authors debated how the term "syndrome" may combine different pathologies [3, 4]. In particular, it has been focused how the phrase OAB could mislead because it "makes it too easy for clinicians to feel they have made a diagnosis when they have not" [5]. Curiously, another syndrome that affects the bladder and is also characterized by "urgency" has been the focus of debate. The bladder pain syndrome (BPS) has in fact recently had a change in the definition although actual wording differs somewhat [6]. In the absence of a universally agreed definition, the International Society for the Study of Interstitial Cystitis

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(ESSIC) defined BPS as "Chronic pelvic pain, pressure or discomfort of greater than 6 months duration perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded" [7]. In practice, patients with symptoms of BPS are screened to exclude other relevant diagnoses or diseases without finding a cause. In the end normal investigations make BPS as a diagnosis of exclusion in patients with urgency to void and bladder pain. It is reasonable to hypothesize that there may be a link between the OABs and BPS considering "urgency" of voiding the symptom of connection between these two syndromes.

To better understand the bladder pain syndrome, we have to focus on pain. Pain is an unpleasant sensation as result of nerve stimulation, with both physical and emotional components. The emotional component was first described by Silas Weir-Mitchell MD in 1864 [8]. In a publication entitled Gunshot Wounds and Other Injuries of Nerves he described how "*As the pain increases… the face becomes anxious, and has a look of weariness and suffering. The sleep is restless… the rattling of a newspaper, a breath of air… give rise to increase of pain.*" The physical component is related to the kind of pain. Pain begins to be felt when its sensation exceeds a threshold. Thus, pain can be divided into high or low threshold based on the point at which sensation becomes painful. It is not the same thing as tolerance, which is how much you can handle.

High-threshold pain is created by a mechanical stimulus (e.g., the puncture of a needle) that activates the nociceptors. It is characterized by the intense cold sensation and involves the presence of chemical irritants.

The low-threshold pains are inflammatory, neuropathic, and dysfunctional. Inflammation activates nociceptors lowering their threshold. Nociceptors can now be activated by less intense stimuli; this creates a change in sensitivity (peripheral sensitization). In the neuropathic pain a neural lesion is the cause of abnormal central processing (e.g., postherpetic neuralgia). Dysfunctional pain is due to an abnormal amplification of sensations without noxious stimulus/inflammation/neural damage (e.g., fibromyalgia). In BPS the pain has the pathognomonic characteristics of the dysfunctional pain.

14.2 Mechanisms in OAB and in BPS at the Bladder Level

Two hypotheses are accepted on the complex mechanisms underlying the genesis of OAB. The urothelium-based hypothesis focuses on changes in urothelial receptor function and neurotransmitter release with consequent change in the sensitivity coupling of the suburothelial interstitial cell network leading to enhancement of involuntary contractions (= detrusor overactivity) [9, 10]. While the myogenic hypothesis identifies as the cause of detrusor overactivity the changes to the excitability and coupling of smooth muscle cells with other myocytes or interstitial cells [11, 12].

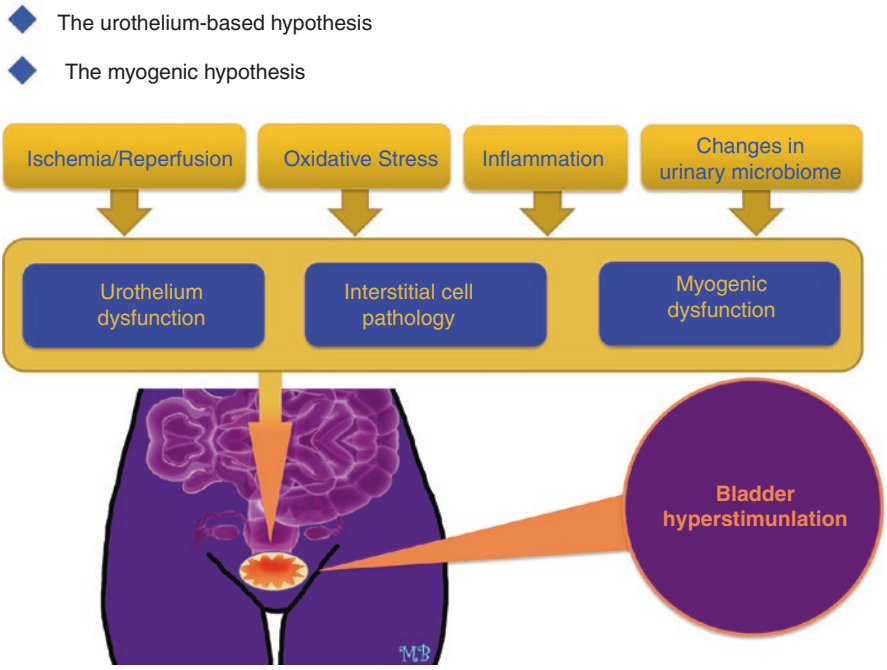

Fig. 14.1 Potential bladder factors involved in OAB

Other potential factors that must be considered in the genesis of OAB are the process of aging, bladder outlet obstruction, bladder ischemia and mucosal injury and microbiome (Fig. 14.1).

In BPS the etiology remains an enigma. However, several etiological factors for BPS have been proposed such as variety of causes as immune cell activation, increased permeability of the urothelium, inhibition of bladder urothelial cell proliferation, autoimmune mechanisms, infection, neurobiology/pelvic cross-talk, urinary toxic agents, hypoxia, and genetics. Symptoms of bladder pain and urinary urgency and frequency are the final common presentation of BPS (Fig. 14.2).

The research on bladder sensitivity focused on a specific cold- and menthol-sensitive thermoreceptor called the transient receptor potential channel of melastatin type 8 (TRPM8). This receptor is a nonselective cation channel localized in primary sensory neurons. In addition to triggering the sensation of cold, these receptors are probably also responsible for the mediation of cold pain and cold-induced urgency [13, 14]. Recent data documented how in patients with OAB and painful bladder the TRPM8 receptor is upregulated in nerve fibers [15]. Moreover, it has been found a significant correlation between its expression level and the worsening of clinical scores in bladder urinary disorders [16].

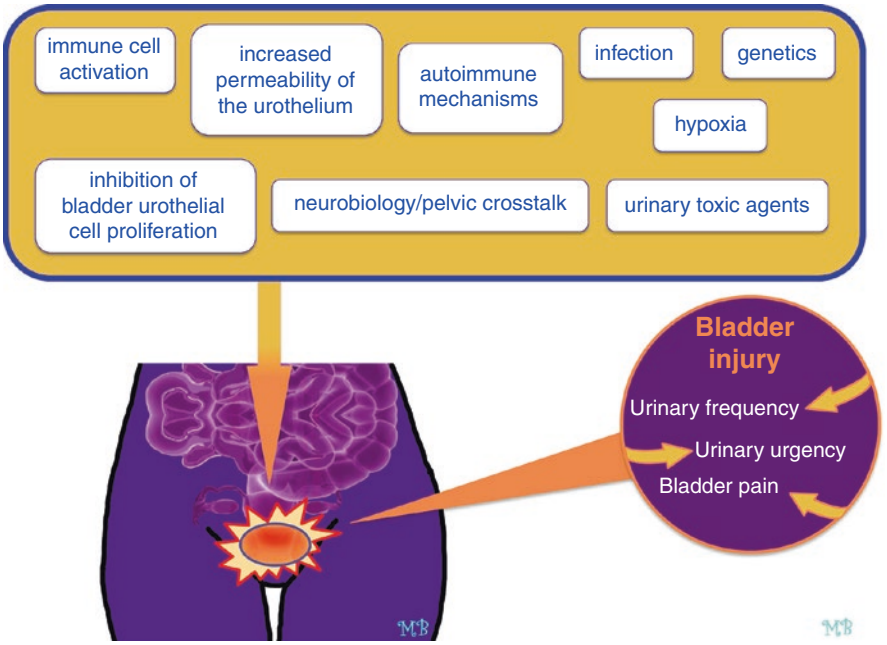

Fig. 14.2 Potential factors involved in BPS

14.3 Mechanisms Involved in the Spinal Cord and in the Central Nervous System

Due to the presence of OAB or BPS, the spinal cord gets persistent peripheral nociceptive signal from the bladder by C-fibers. This continuous stimulus gains some changes. A first change is the recruitment/activation of N-methyl-D-aspartame (NMDA) receptors that are easy to trigger. Then, the reduced firing threshold enhances all neuronal responses, including those derived from low-threshold input signals that normally generate non-painful sensations (Fig. 14.3).

Finally, there is the overlap with the fibers involved in the sensitivity of other pelvic organs systems (e.g. bowel). These changes brought about by the continuous arrival of stimuli from the bladder create spinal hypersensitivity.

From the spinal cord the input signals arrive to the central nervous system where due to the convergence of neural circuits and the integration at the spinal level occurs the transition from acute to chronic pain. In this situation peripheral nerves function is normal, but there is a change in function in central neuron that results in a condition called central sensitization. The International Association for the Study of Pain defines central sensitization as "increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input" [17]. This process facilitates normally subthreshold action

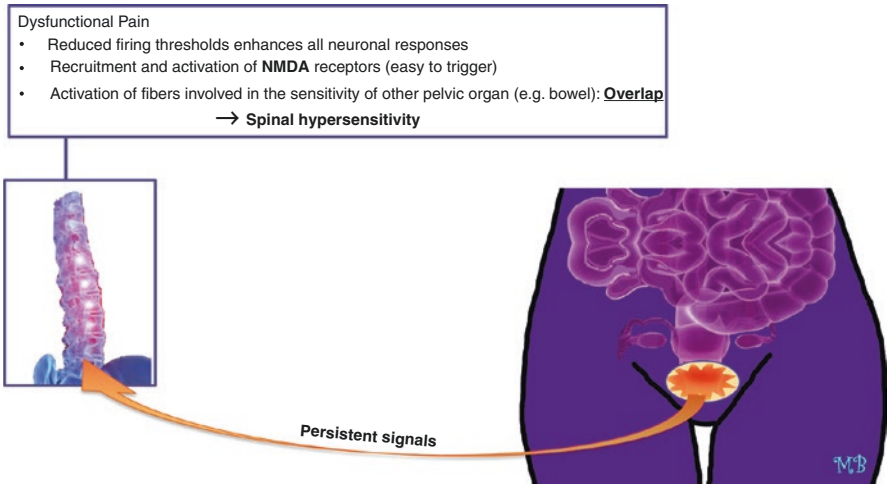

Fig. 14.3 Changes in the spinal cord due to persistent bladder signals

potentials leading to the activation of central neural circuits. Due to the convergence of neural circuits and the integration of larger spatial field in the spinal cord, it is possible to have the extension of symptoms to areas remote from the conditioning C-fiber stimulus [18]. In a condition of central sensitization, it is usual to feel pain also in case of non-painful stimuli (= allodynia); moreover pain is felt with a higher intensity (= hyperalgesia). This condition of hypersensitivity may increase the perception of sensations such as cold, warmth, touch, and of visual or auditory stimuli [19, 20]. This change in perception may be linked to central sensitization in conditions like overactive bladder and bladder pain syndrome.

Moreover, the overlap of information between fibers from bladder and those involved in the sensitivity of other pelvic organs systems (e.g., bowel) in the spinal cord and overlap of information in the central nervous system rationalize the visceral organ cross-talk (Fig. 14.4).

The overlap between the bladder and other pelvic organs has been documented by clinical studies supporting the experimental findings of animal models [21, 22]. This visceral organ cross-talk is a very common clinical finding. It is well known how a rectal distension can generate change in bladder capacity, bladder sensation, and detrusor overactivity. While straining to defecate and constipation can impair bladder emptying, increasing severity of voiding and storage symptoms. Thus, patients with diseases not well understood like irritable bowel syndrome, bladder pain syndrome, chronic pelvic pain, vulvodynia, chronic prostatitis, and fibromyalgia may have mechanisms not different from those described and the visceral cross-talking is a mechanism that may explain how patients with a symptom to a specific organ may generate disturbs to others pelvic organs.

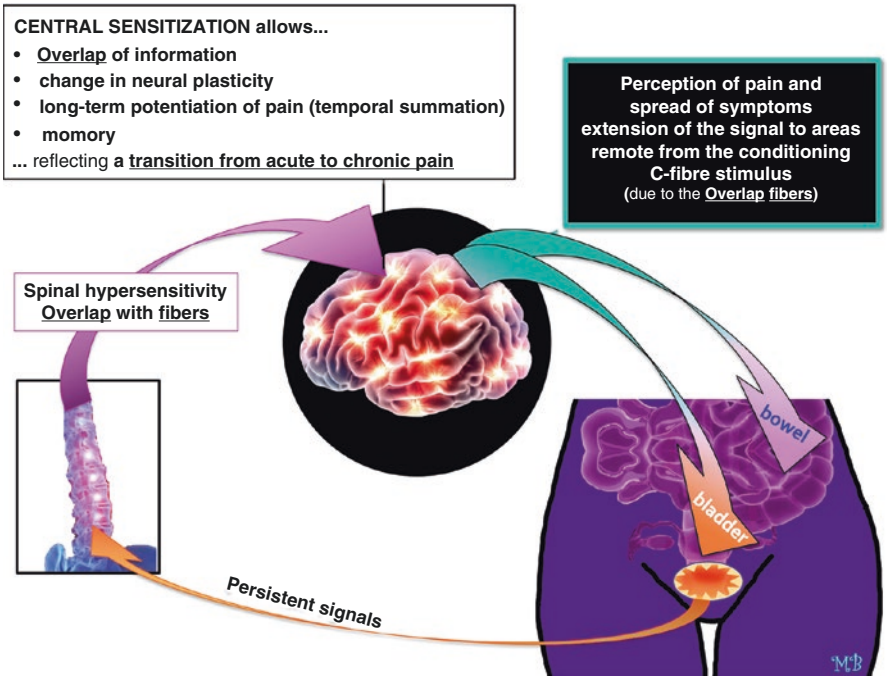

Fig. 14.4 Overlap of information with fibers involved in the sensitivity of other pelvic organs systems (e.g., bowel) in the spinal cord and overlap of information in the central nervous system rationalize the visceral organ cross-talk

14.4 Mechanism of Central Sensitization and Clinical Evidences

Central sensitization develops following persistent signals from nociceptors that originate from cutaneous, muscular/joint, and visceral pain. However, central sensitization allows the perception of pain without the presence of tissue damage. Due to central sensitization non-painful signals can generate pain (= allodynia), and painful stimuli provoke a pain of higher intensity (= hyperalgesia) [23]. This neural hypersensitivity might also increase with visual and auditory stimuli [20]. Central sensitization may explain several clinical chronic pain and somatic conditions that usually have no certain diagnosis and which are often exclusion diagnoses [24, 25]. So it is not surprising that Warren et al. documented how a population of women with pelvic pain with urinary features, frequency, and bladder pain were more likely to develop bladder pain syndrome [26]. Moreover, central sensitization can explain how some stimuli that are "normal" for the majority of the population for some categories of patients became triggers for pain or involuntary bladder contractions. Indeed, virtually any sensory non-painful experience that allows to central sensitization may generate increased excitation or reduced inhibition [23]. Woolf described

the clinical characteristics to gain the diagnosis of central sensitization [23]. In particular, it is necessary to have:

- Pain mediated by low-threshold Aδ-fibers
- Spread of pain sensitivity to non-pathological areas
- Aftersensations
- Enhanced temporal summation
- Maintenance of pain by non-painful low-frequency stimuli

Currently it is possible to assess clinical manifestation of central sensitization in humans only by psychophysical laboratory techniques [27, 28]. In particular, the increase in pain perception in response to application of a repetitive series of brief noxious stimuli delivered at constant intensity is called temporal summation. This is the main accepted index for measurement of central sensitization [29]. In a series of 20 adult women Reynolds et al. demonstrated that women with OAB refractory to secondary level therapies presented greater thermal cutaneous temporal summation than women without OAB symptoms. This suggests that central sensitization, at least in a group of patients with severe OAB, could be an underlying factor contributing to the genesis of OAB itself [30]. A further step was achieved by demonstrating that in women with more severe OAB symptoms, one had also increased overall body pain intensity (= hyperalgesia), and increased general somatic symptom burden. This data strongly suggest how central sensitization has a role at least in patients with severe OAB [31]. The finding that only women undergoing third-line OAB treatment had elevated thermal temporal summation suggests there may be pathophysiological differences in some women with OAB, make these patients a separate category of OAB [32].

14.5 Links Between OAB and BPS

Clinical experience shows us that some patients with a well-known diagnosis of OAB report the onset of a new bladder pain sensation over time. Usually the clinical question is to exclude new pathologies that could cause this pain. However clinical investigations reveal no clear etiology for the pain. In these cases, the clinician has the feeling that from an OAB the patient is switching to a BPS. In a female population affected by overactive bladder but without bladder pain syndrome, Kovalik et al. documented how painful urgency and/or painful filling were reported and associated with greater pain intensity typical of hyperalgesia and increased somatic symptom burden. Due to these findings these authors concluded that overactive bladder and interstitial cystitis/bladder pain syndrome diagnoses may represent a continuum of bladder hypersensitivity with predominating symptoms of urgency and frequency on one end and pain as predominating on the other end [33]. In these cases, central sensitization might explain progression from increased urinary frequency (in some women) to painful BPS and hint that some of the urinary symptoms of OAB might reflect the presence of central sensitization as an underlying

mechanism. As such, the concept of central sensitization might explain the mechanism of transition from OAB to BPS. This mechanism can be very important especially in those patients with central sensitization-related comorbidities where the visceral organ cross-talk may switch on pain in areas other than the bladder. Data reported by Asfour V et al, clearly show how OAB and bladder pain are on the same spectrum of disease symptoms, and bladder pain plays a key role in OAB [34]. Authors documented how bladder pain and nocturia were reported in 95% of 3428 patients affected by OAB. This would seem reasonable as both are C nerves syndromes and they both result in frequency and urgency. Conclusion was that "OAB symptoms appear to be related to bladder pain and this could suggest a joint etiology or a spectrum ranging from pure OAB to pure bladder pain." These data, as well as other, may indicate the reason for some patients with OAB who do not respond to treatment [33, 34].

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Part III

Chronic Pelvic Pain Syndrome Treatment

Neuropharmacology of Pain

15

Diego Fornasari

15.1 Introduction

Pain, in its acute nociceptive form, is essentially a physiological phenomenon aimed at signaling to individuals exposure, or possible exposure, to forms of high-intensity energy that can damage them, in particular mechanical energy (the impact with a moving body), thermal energy (too hot, too cold), and chemical energy (acidic or basic pH). Pathological pain is identified, with the exception of acute inflammatory pain, with chronic pain, a pain that persists or recurs over time, but which is essentially characterized by a fundamental aspect: the alteration of one or more rules of physiological nociception. Although there are hundreds of pathologies that are dominated by pain, the pathogenetic mechanisms of pain, in their essential aspects, are in extremely limited numbers and identify as many types of pathological pain. In terms of pathogenetic mechanisms, we recognize inflammatory pain, neuropathic pain, mixed pain (that is, with pathogenic mechanisms that can be traced back to both inflammatory and neuropathic pain), dysfunctional pain (for example, fibromyalgia), and mechanical-structural pain (e.g., non-inflamed arthritis). Pelvic pain does not escape this pathogenetic framework.

The recognition of the specific pathogenetic mechanisms along with the identification of the violated nociceptive rules is essential to establish a correct pharmacological approach.

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15.2 Physiology of Pain in a Pharmacological Perspective

The process of painful stimuli is organized into five essential phases: transduction, conduction, modulation, transmission, and perception [1–3].

Transduction is the process that converts forms of high-intensity energy, which are potentially dangerous, into an electrical signal, the generator potential, which in turn favors the onset of the action potential. This phenomenon occurs in the peripheral terminals of the primary, somatic and visceral afferent nociceptive fibers, which have their bodies in the dorsal ganglia. The primary nociceptive neurons of the dorsal ganglia, better known as nociceptors, are high-threshold neurons, specialized in responding to stimuli of high intensity. They possess a peripheral fiber, which innervates the tissues, and a centripetal fiber which penetrates into the spinal cord and enters into synaptic contact with one or more spinothalamic neurons. Their peripheral terminals express in the plasma membrane highly specialized transducer proteins, many of which are ion channels that open in response to specific high-energy stimuli. The influx of calcium and sodium determines the depolarization of the terminal.

Conduction is the phase in which the action potentials travel along the axons to reach the spinal cord. Several isoforms of voltage-gated sodium channels are known, with Nav 1.7, 1.8 and Nav1.9 which are the most abundantly expressed in nociceptors. Nociceptors can have unmyelinated fiber (C fiber) or small myelinated fiber (Aδ fiber). C fibers, which have a slower conduction, are probably those most involved in chronic pain. When action potentials reach nociceptor terminals in the dorsal horns of the spinal cord, N-type voltage-gated calcium channels open and calcium inside the terminal promote the fusion of synaptic vesicles and neurotransmitter release. *Transmission* corresponds to synaptic communication between first- and second-order neurons. The synapse between the nociceptor, or first-order neuron, and the spinothalamic neuron, or second-order neuron, is mainly glutamatergic. In acute nociceptive pain, glutamate binds mainly to AMPA receptors, which are ligand-gated ion channels, highly permeable to sodium ions. They depolarize second-order neurons, triggering the train of action potentials that will reach the thalamus. Spinal synapse activity is finely controlled by several mechanisms that are part of pain *modulation* processes. In fact, not all the impulses coming from the periphery reach the thalamus because the synaptic transmission in the spinal cord is regulated by the action of local interneurons and by projections that descend from the brain stem. The main neurotransmitters inhibiting dorsal horns are opioids, noradrenaline, serotonin, anandamide, and GABA. The opioid system is the main endogenous analgesic system. Opioids produce analgesia by multiple actions in the brain, in the brain stem, in the spinal cord, and, in some cases, also in the peripheral terminals of nociceptors, in the course of inflammation. Endogenous opioids bind to G protein-coupled receptors, which are traditionally divided into three classes: μ, δ, and κ receptors. More recently, a fourth receptor has been added which with its ligand constitutes the nociceptin system. All opioid receptors are coupled to inhibitory G proteins and receptor activation inhibits adenylate cyclase and intracellular

generation of cAMP. However, the coupling of opioid receptors to ion channels for potassium and calcium is believed to be the most important mechanism by which both endogenous and exogenous opioids produce analgesia [4]. In particular, in the dorsal horns of the spinal cord the great majority of opioid receptors is of the μ type, with a presynaptic localization, about 70%, on the spinal terminals of the C and Aδ fibers coming from the periphery. The remaining 30% is located postsynaptically, on the dendrites of spinothalamic second-order neurons. At presynaptic level, the μ receptors are predominantly localized on the C fibers, with a priority role in the control of "slow" pain and especially of chronic pain, of which the C fibers are mainly responsible. Physiologically, endogenous opioids are released in the dorsal horns mainly from interneurons, in turn stimulated by the descending pathways coming from the brain stem, with particular reference to the periaqueductal gray (PAG). Mu receptors have also been identified at this level where their activation unlocks the descending pathway, confirming the supra-spinal contribution of opioids in analgesia. At the spinal level, the presynaptic μ receptors inhibit the opening of N-type calcium channels, preventing the entry of calcium and the vesicular release of neurotransmitters. On the postsynaptic neuron the μ receptors cause the opening of potassium channels, with the outflow of these ions and consequent hyperpolarization and reduced excitability of the second-order neuron. Figuratively, opioids render the first-order neuron "mute" and the second-order neuron "deaf," achieving a profound inhibition of the spinal synapse that underlies their powerful analgesic activity. The *perception* of pain is realized when nociceptive stimuli reach the sensory cortex and is the result of complex phenomena of integration with areas of vegetative and emotional life that make pain "a subjective and multidimensional experience, with an important impact on the physiological state and psychology of the individual" (IASP).

15.3 Pathological Pain

15.3.1 Inflammatory Pain

As mentioned above, pathological pain is characterized by the alteration of some mechanisms of physiological nociception. Modification of the neural structures occurs in acute and, above all, chronic inflammatory pain in which nociceptors at the level of peripheral terminals lower their activation threshold and increase their excitability. This phenomenon is known as peripheral sensitization and is mainly the result of the phosphorylation of numerous molecules peripherally involved in the processing of painful stimuli, including the TRPV1 and the Nav 1.8 voltage-dependent sodium channel [5]. Following phosphorylation, TRPV1 is activated at 37 ° C, instead of at 43 ° C, and Nav 1.8 decreases the duration of its refractory period, opening more frequently and allowing the conduction of high-frequency action potentials. The phosphorylation of these substrates is the consequence of the activation of different kinases by sensitizing agents that operate through their own

membrane receptors, with particular reference to prostaglandins and cytokines, released by inflammatory cells that infiltrate the inflamed tissue. Thus, the pain evoked by generally non-algogenic stimuli (allodynia) or even the spontaneous pain that accompany inflammation is the expression of a reduction or abolition of the nociceptor stimulation threshold, caused by the presence of sensitizing agents. Thus, blocking the synthesis of these agents becomes an essential pharmacological strategy for the treatment of inflammatory pain.

15.3.2 Neuropathic Pain

Neuropathic pain is the result of the lesion or pathology of peripheral, spinothalamic or thalamocortical nociceptive neurons. The peripheral fiber of the dorsal neuron is more frequently affected, with consequent structural and functional modifications affecting both the lesion site and the proximal fiber that reaches the spinal cord from the ganglion. At the point of the lesion, where the fiber can be interrupted, there is a functional reorganization of the proximal stump of the fiber, with the appearance of Nav 1.3 sodium channels and with the progressive reduction of the potassium channels. NaV 1.3 are present during the embryonic life and are particularly excitable, whereas potassium channels are responsible for hyperpolarization and therefore for electrical stabilization of the neuron. The global result of these two modifications is that the DRG becomes much more excitable. It is interesting to note that the expression of some relevant potassium isoforms is under the negative control of BDNF and that some tumors, such as those of the prostate, pancreas, and lung, are able to produce BDNF. Thus, the pathogenetic mechanisms of neuropathic pain are enriched and complicated by the active biochemical contribution of the tumor. Painful stimuli no longer originate from nociceptive terminals, but from the ectopic site that formed at the point of injury. The ectopic site, due to its electrophysiological characteristics, discharges at very high frequency, sometimes spontaneously, sometimes because stimulated by external stimuli [6]. Functional modifications also affect the fiber that reaches the spinal cord. At the presynaptic level, on the fiber terminal, an increase, up to 10 times, in the number of N-type calcium channels occurs. This involves a massive calcium entry and a huge glutamate release, also supported by the high discharge rate of the peripheral fiber. Therefore, in neuropathic pain, blocking the activity of voltage-dependent sodium channels and blocking N-type calcium channels are first-line pharmacological strategies.

15.3.3 Spinal Transmission and Central Sensitization

Whatever the cause in pathological pain there is a massive release of glutamate in the spinal synapse with a greater postsynaptic depolarization. This persistent depolarization removes the Mg^{2+} voltage-dependent blockade of NMDA receptors, the other class of glutamate receptors expressed in second-order neurons, which are

extremely permeable to calcium ions. Activation of the NMDA receptor is an essential step in central sensitization, a phenomenon that always accompanies chronic pain, in which the spinothalamic neuron lowers its activation threshold and transmits nociceptive stimuli more easily. In fact, calcium, acting as a second messenger and activating kinases, participates in phenomena of pathological remodeling of the synapse and spinothalamic neuron [7, 8]. In chronic pain spinal synapse represents a primary pharmacological target to reduce nociceptive transmission and limit the phenomena of synaptic plasticity that worsen the painful state.

15.4 Pharmacological Strategies for the Treatment of Pain

The pharmacological strategies for treating pain should be based on the pathogenetic mechanisms that generated it. Thus, we may recognize four different drug classes with the following actions: counteracting peripheral sensitization, inhibiting the propagation of action potentials, inhibiting spinal transmission and central sensitization, and enhancing the action of descending pathways.

15.4.1 Drugs Acting on Peripheral Sensitization

These are drugs that inhibit the synthesis of prostanoids and cytokines, which are mainly responsible for peripheral sensitization. NSAIDs, COXIBs, and corticosteroids belong to this group. NSAIDs and COXIB inhibit COX-1 and COX-2 with different selectivity and potency. They are appropriate in all forms of inflammatory pain. Corticosteroids have different mechanisms of action, but their anti-inflammatory activity depends mainly on the inhibition of the transcription factor NFκB. NFκB regulates gene transcription and therefore the expression of several pro-inflammatory cytokines, including IL-1, IL-6, TNFα, INF-γ, some enzymes, including COX-2 and inducible NOS, and proteins variously involved in inflammation. Corticosteroids are often used for their anti-edema properties in neuropathic pain, thus reducing the compression on nerve fibers.

15.4.2 Drugs Acting on Nerve Fibers

These are drugs that act directly on the damaged nerve fiber, counteracting the propagation of action potentials and the abnormal release of neurotransmitters at the level of the spinal synapse. They act on voltage-dependent sodium channels and on N-type voltage-dependent calcium channels. They are appropriate for neuropathic pain and mixed pain. Voltage-dependent sodium channel blockers arise as anticonvulsants, anti-arrhythmics, or as local anesthetics such as carbamazepine, oxcarbazepine, lamotrigine, and lidocaine. The drugs that act on the N-type calcium channels are pregabalin and gabapentin. Despite the name, their

mechanism of action does not involve the gabaergic system, but even defining them as blockers is certainly inaccurate. As previously described, in the lesion of the first-order neuron there is a modification which also affects the proximal fiber entering the spinal cord, with an increase up to 10 times in the expression of the N-type calcium channels. This phenomenon is believed to be due to an accumulation of the channel in the cell membrane due to defects in its cellular "trafficking," i.e., the channel is introduced into the membrane but is no longer removed. In this traffic block, specific for calcium channels, the α2δ accessory subunit could play a role: in fact it is the α2δ subunit that makes contact with the extracellular matrix and acts as an anchor that prevents channel internalization. The gabapentinoids, also known as ligands of the α2δ subunit, by binding to these subunits would favor the un-anchoring and internalization of the channel. So these drugs do not block N-type channels but promote a reduction in their number by restoring their cellular traffic, thus reducing the release of glutamate in the synapse [9]. This mechanism of action underlies the fact that these are not fast-acting drugs, they must be administered for sufficiently long periods of time and are not appropriate for inflammatory pain. Ziconotide, a synthetic analogue of ω-conotoxin, a peptide produced by a marine snail, is a direct blocker of the opening of the N-type calcium channels. It is a first-line drug for intrathecal administration, both for nociceptive and neuropathic pain.

15.4.3 Drugs Acting on the Spinal Synapse

This group of drugs interferes with spinal synaptic transmission and through this action counteracts the establishment and effects of sensitization.

15.4.3.1 Paracetamol

Paracetamol is generally classified among NSAIDs, with which it shares the antipyretic and analgesic actions, but not the anti-inflammatory action. Its belonging to this pharmacological class depends on its ability to "in vitro" inhibit COX-1 and COX-2. However its power of inhibition is very small compared to other members of the class. Furthermore the action of paracetamol is inhibited in situations of high concentration of peroxides, as typically happens in inflamed tissues. This would explain the absence of anti-inflammatory effects of paracetamol and would suggest that also its analgesic effects may rely on molecular and cellular mechanisms distinct from those of NSAIDs. Paracetamol easily crosses the blood–brain barrier and is metabolized in the CNS in a compound known as AM 404. The chemical structure of AM404 is very similar to that of anandamide, one of the most important endogenous cannabinoids, and this is basis of its mechanism of pharmacological action. AM404 is a weak agonist of the cannabinoid receptors CB1 and CB2, but above all it is an inhibitor of the transporter responsible for the reuptake of anandamide, causing its synaptic accumulation and prolonging its pharmacological effects. Therefore paracetamol, through its metabolite AM404, would enhance the

endocannabinoid tone in numerous areas of the nervous system, including the dorsal ganglia and the dorsal horns of the spinal cord, where the metabolite performs part of its analgesic activity [10].

15.4.3.2 Opioids

Opioids constitute the reference pharmacological class in the treatment of cancer pain and pain related to surgery. However, in the last 20 years, because of their high analgesic activity, opioid use has been extended to chronic pain [4]. The opioid drugs used in analgesia are frequently full μ receptors agonists. These include morphine, oxycodone, hydromorphone, fentanyl, and methadone. These opioids are generally referred as strong opioids. All these drugs, although having comparable efficacy, where the efficacy coincides in this case with the maximum possible analgesic response, have different potencies. This means that to produce the same analgesic effect they must be used at dosages sometimes very different from each other. The different potency of opioid drugs can be a problem when it is necessary to switch from one drug to another, to so-called opioid rotation, a relatively frequent occurrence in the treatment of cancer pain. For this reason the concept of "equianalgesia" was introduced, which underlies the fact that to obtain the same analgesia, passing from one opioid to another, different dosages must be used according to a conversion system, dictated more by clinical practice than by rigorous pharmacodynamic and pharmacokinetic arguments, that consider morphine as the reference opioid for calculations. In both cancer and non-cancer pain, partial agonists are frequently used and are generally referred as weak opioids. In fact these drugs activate μ receptors, but they produce a reduced maximal effect than full agonists. The reduced efficacy of weak opioids is often referred as "ceiling effect." Interestingly, buprenorphine, a weak opioid, has a higher potency than morphine. So, at the higher doses, buprenorphine will show "a ceiling effect" compared to morphine, but at lower doses the analgesic effects of buprenorphine are higher than morphine. Other partial agonists are tramadol and tapentadol, which compensate for their modest activation of the μ receptors with a second mechanism of action: the inhibition of the reuptake of serotonin and noradrenaline, or of the noradrenaline alone, respectively. Codeine, which has always been considered the most typical of weak opioids, is simply a prodrug that must be converted to morphine through the action of CYP450 2D6. From this brief discussion it is clear that the old distinction between weak and strong opioids is greatly simplifying and of little clinical use, especially in chronic non-cancer pain.

15.4.3.3 Cannabinoids

The endogenous cannabinoid system is particularly widespread and presides over various functions including the control of nociception. For this reason its components, receptors, ligands, and enzymes, are strategically located in essential nodes for the control of pain, such as the dorsal ganglia, the dorsal horns of the spinal cord, the PAG, the thalamus, and the cingulate cortex. In the spinal synapse the endocannabinoid system could physiologically function "on demand," basing its activity on

retrograde transmitters, acting as a brake on nociceptive transmission. The role of phytocannabinoids and synthetic cannabinoids in the treatment of pain is the subject of numerous studies, especially with a view to their use in combination with opioids. Their possible use in some types of neuropathic pain is promising and widely debated, but no clear clinical evidence have still emerged [11, 12].

15.5 Drugs Potentiating the Activity of Descending Pathways

The pathways descending from the brainstem mainly release serotonin and noradrenaline, which, directly or through the activation of interneurons, inhibit the spinal synapse. In particular, norepinephrine can be released from fibers descending from the *locus coeruleus*, the most important noradrenergic nucleus of the CNS. Norepinephrine binds to α2-adrenergic receptors located on the presynaptic membrane of the spinal synapse, which inhibit calcium channels and therefore glutamate release. The pharmacological manipulation of the descending pathways can be obtained according to three different strategies: increasing the discharge of the descending pathways, prolonging the action of serotonin and noradrenaline in the spinal synapse, and mimicking their action. Regarding the first aspect, there are several drugs that possess the property, often ancillary, of activating the descending pathways, or removing a tonic inhibition exerted on them by inhibitory interneurons. For instance, both opioids and gabapentinoids by acting in the brainstem can inhibit inhibitory interneurons whose activity prevents the discharge of descending pathways: an inhibition of an inhibition. A direct activation can be obtained with paracetamol, especially if given as i.v. bolus, and cannabinoids; both activate central TRPV1 expressed by PAG neurons, causing their depolarization. The second strategy is the best known: the use of serotonin and norepinephrine reuptake inhibitors, namely tricyclic antidepressants such as amitriptyline or SNRIs such as duloxetine and venlafaxine. It should be stressed that the effects of these drugs is independent of their action on the mood and that the onset of their analgesic activity is not delayed as their antidepressant activity in the psychiatric setting. The third strategy mainly concerns agonist drugs directly stimulating α2-adrenergic receptors expressed in the spinal cord: clonidine and dexmedetomidine.

15.6 Conclusions

The knowledge of the pathogenetic mechanisms underlying pain is an essential prerequisite for the appropriate use of analgesic drugs. On the other hand, the definition of the pharmacological classes on the basis of their targeted pathogenetic mechanisms is a need to maximize therapeutic results, minimizing adverse effects.

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Pharmacological Treatment of Bladder Pain Syndrome/Interstitial Cystitis

16

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Abbreviations

ATP	Adenosine triphosphate
AUA	American Urological Association
BPH	Benign prostatic hyperplasia
BPS	Bladder pain syndrome
CPP	Chronic pelvic pain
EAU	European Association of Urology
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
IC	Interstitial cystitis
IgE	Immunoglobulin E
LUTS	Lower urinary tract symptoms
PDE5-I	Phosphodiesterase 5 inhibitors
UTI	Urinary tract infections

16.1 Introduction

Chronic pelvic pain (CPP) is defined as a non-cyclic pain with a duration of at least 6 months. This form of painful condition may definitely worsen patients' quality of life [1].

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Certain researchers also suggested that CPP syndrome might be a form of bladder pain syndrome/interstitial cystitis (BPS/IC). In fact, in 2007 the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) began to group together BPS/IC and chronic prostatitis/CPP syndrome under a single umbrella term: urologic chronic pelvic pain syndromes. According to this idea, in the last decades the scientific community tried to circumscribe chronic bladder pain and IC in a single entity, thus generating scientific and clinical confusion both from a diagnostic and from a therapeutic point of view.

Recently, to ensure a systematic approach and to provide clearness in the clinical practice, the International Continence Society set out a series of four domains in CPP syndromes, based on the pelvic organs: lower urinary tract domain, female genital domain, male genital domain and gastrointestinal domain. In this attempt of standardization, the lower urinary tract domain includes both bladder and urethra while worldwide the definitions for BPS and IC are not yet completely standardized [1].

Actually, the classic Hunner's disease is a specific and well-defined pathology and fulfils the requirements for the denomination of "interstitial cystitis". Evidences are accumulating on the unique and outstanding features of this clinical entity, as the therapeutic requirements differ significantly between this and other phenotypes of IC [2].

In this chapter, we would examine the pharmacological options in the treatment of BPS/IC, both oral and intravesical, and thus providing a critical analysis of what is currently established by internationally recognized guidelines and by the most significant publications on this issue.

16.2 Oral Therapy

16.2.1 Antidepressants

Antidepressants are often used in the treatment of many forms of chronic pain. Their mechanisms are variable and their action on pain may be independent from antidepressant effect.

16.2.1.1 Amitriptyline

Amitriptyline is a tricyclic antidepressant that inhibits serotonin and noradrenaline reuptake and blocks acetylcholine and histamine (H1) receptors. Anticholinergic effect may alleviate urinary urgency and frequency and reduces inflammatory response; moreover, the inhibition of these neurotransmitters has an analgesic effect [3]. The suggested dose of amitriptyline is 10 mg to 75–100 mg daily and can be used in association with gabapentin [4]. Common side effects include dry mouth, constipation and drowsiness.

(Level of Evidence: 2. Grade of Recommendation: B)

16.2.1.2 Duloxetine

Duloxetine is a serotonin and noradrenaline reuptake inhibitor. This drug can improve stress urinary incontinence and is also used in the treatment of neuropathic pain [5]. The suggested dose is 20–80 mg daily. However, there are insufficient data to demonstrate its efficacy in chronic pelvic pain syndrome [6].

(Level of Evidence: 4. Grade of Recommendation: C)

16.2.2 Pentosan Polysulphate Sodium

In patients with BPS the glycosaminoglycan (GAG) layer of the bladder urothelium can be damaged; a defective GAG layer is hypothesized to be one important mechanism for BPS. Pentosan polysulphate sodium (PPS) is a synthetic sulphated polysaccharide that aims to restore the damaged GAG layer and can inhibit histamine release from mast cells. PPS is available in oral and intravesical formulation and is approved by FDA for BPS [7]. The suggested dose is 300–900 mg daily and it can be administered in association with subcutaneous heparin. Side effects include thrombocytopenia and alopecia. Many studies have demonstrated its efficacy and its ability to improve pain and urinary symptoms [8].

(Level of Evidence: 1. Grade of Recommendation: D)

16.2.3 Antihistamines

In patients with BPS there can be an increased number of mast cells in the bladder wall, suggesting that histamine may be responsible for the development of BPS. Blocking histamine release can lead to reduced inflammatory response, thus improving pain and urinary symptoms.

16.2.3.1 Hydroxyzine

Hydroxyzine is a histamine H1 receptor antagonist and it also has anticholinergic and slight sedative properties. Many patients show improvement from their baseline symptoms [9]. The suggested dose is 25 mg to 50–75 mg daily at bedtime. Common side effects include sedation and drowsiness.

(Level of Evidence: 1. Grade of Recommendation: D)

16.2.3.2 Cimetidine

Cimetidine is a histamine H2 receptor antagonist, mostly used for the treatment of peptic ulcer disease. Cimetidine improves pain and nocturia, though does not lead to histological changes of the bladder mucosa [10]. The suggested dose is 300–400 mg twice a day. Side effects include dizziness and headache.

(Level of Evidence: 3. Grade of Recommendation: C)

16.2.4 Analgesics

Analgesics are one of the most used drugs in the treatment of BPS. They often represent the first-line treatment in people suffering from chronic pain and patients may use these drugs independently. Analgesics include many heterogeneous compounds, such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS), cyclooxygenase (COX) inhibitors, opioids and corticosteroids.

16.2.4.1 Acetaminophen

Acetaminophen (paracetamol) is an analgesic with antipyretic activity. Though it is well tolerated, its efficacy is limited and should be used in association with other compounds to enhance their effect.

16.2.4.2 NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)

NSAIDs include many compounds that inhibit COX-1 and COX-2 enzymes, while COXIB are highly selective COX-2 inhibitors (such as celecoxib and etoricoxib). The COX-1 enzyme usually regulates gastric mucosal integrity and both renal and platelet function; its block is the typical cause of NSAIDs complications. On the contrary, COX-2 enzyme is inducible and it is generated as a result of tissue damage and it is involved in inflammatory response. Despite this, there is little evidence for a role of NSAIDs in the management of chronic pelvic pain, though they can be used as first-line analgesics [11]. These drugs should be avoided in patients with increased risk of gastric complication or chronic kidney failure; likewise, COX-2 selective drugs should be avoided in patients with known cardiovascular disease.

16.2.4.3 Opioids

Although they are mainly used in the treatment of cancer pain, opioids have a role in the management of chronic pain [12, 13]. Opioid treatment should be prescribed only after other reasonable treatments have been tried and failed. Due to their potentially life-threatening side effects, the decision to instigate long-term opioid therapy should be made by an appropriately trained specialist [11]. The common side effects of opioids include sedation, nausea, constipation and confusion. Respiratory depression is rare if they are used as prescribed. Morphine is the first-line drug, though there is no evidence that one compound is better than another. Other opioids include fentanyl, methadone, oxycodone, hydromorphone, codeine and tramadol.

(Level of Evidence: 4. Grade of Recommendation: C)

16.2.4.4 Corticosteroids

There is insufficient data for the long-term use of corticosteroids and their side effects can be serious. However, intravesical injection of corticosteroids may be considered.

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.5 Immunosuppressant

BPS could have an autoimmune component which leads to an inflammatory response: in fact, cytokines and chemokines are significantly increased in urine and bladder tissues from BPS patients. The modulation of immunological response is a therapeutic option to reduce urinary and pain symptoms.

16.2.5.1 Cyclosporine A (CyA)

Cyclosporine A (CyA) is a widely known immunosuppressive drug, mostly used in transplantation and in autoimmune disease. It inhibits calcineurin and suppresses T cell activity and cytokine release, thus interfering with the production of IL-2 and T cell-related immune response. CyA treatment reduces voiding frequency and mean voided volume [14]. Evidences suggest that CyA is more effective in patients with Hunner's lesion than in those without [15]. Despite it is a recommended therapy by the AUA, it is currently without FDA approval. Oral treatment with CyA should begin with a starting dose of 2.5–5.0 mg/kg/day and a maintenance dose of 1.5–3.0 mg/kg/day. Side effects are common and include hypertension, increased serum creatinine level and alopecia.

(Level of Evidence: 3. Grade of Recommendation: C)

16.2.5.2 Azathioprine

This molecule has shown efficacy in reducing both pain and lower urinary tract symptoms [16]. The suggested dose is 50–100 mg daily and common side effect is nausea.

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.5.3 Methotrexate

Low dose oral methotrexate can improve pain in patients with BPS but does not improve urinary symptoms [17].

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.5.4 Suplatast Tosilate

Suplatast tosilate (IPD-1151T) is an oral immune regulator that suppresses helper T cell-mediated allergic processes, including IgE production and eosinophilic inflammation. This compound may significantly increase bladder capacity while decreasing voiding and pain symptoms [18]. However, there are insufficient data to justify its use, though it is commonly prescribed in Japan for the treatment of BPS.

(Level of Evidence: 1. Grade of Recommendation: D)

16.2.6 Antibiotics

UTIs might play a role in the genesis of LUTS. The exclusion of UTIs is a key step in the management of LUTS but sometimes persistent LUTS may originate from undetected UTIs. It is important to note that most BPS patients have been treated

with empiric antibiotics prior to diagnosis. Antimicrobial therapy (quinolones or tetracyclines) has a moderate effect on total pain, voiding and QoL scores [19]. Patients responding to antibiotics should be maintained on medication for 4–6 weeks as recommended by EAU guidelines.

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.7 Anticonvulsants

Anticonvulsants are widely used in the treatment of neuropathic and chronic pain. They exert their effects in different ways and some compounds have more than one mechanism of action. They can also be used in association with other classes of medication to enhance their effect on pain relief, while reducing doses and consequent side effects. They include gabapentin, pregabalin and carbamazepine.

16.2.7.1 Gabapentin

This anticonvulsant drug induces activation of α2δ subunit of the voltage-gated calcium channels, modulating the release of neurotransmitters involved in nociception. It has favourable action profile, including few side effects and lack of interactions with other medications [20]. The suggested dose is 300–1200 mg/day and side effects include drowsiness and peripheral oedema.

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.7.2 Pregabalin

It has similar structure as gabapentin and has similar mechanism of action. Although it is commonly used in neuropathic pain disorders, pregabalin is not effective for the treatment of BPS.

16.2.7.3 Carbamazepine

Carbamazepine is a sodium channel blocker mainly used in the treatment of epilepsy and neuropathic pain. It is no longer a first choice drug due to its side effects.

16.2.8 New Emerging Compounds

16.2.8.1 Rosiptor (AQX-1125)

This compound activates SH2-containing inositol-5′-phosphatase (SHIP1), which modulates the PI3K pathway involved in chronic inflammation. SHIP1 has anti-inflammatory effect by downregulating the PI3K pathway. This is a promising medication, currently under evaluation in a phase III study. Women taking AQX-1125 at the dose of 200 mg daily reported significant reduction in their subjective bladder pain and an improvement in urinary symptoms. The most reported side effects were dyspepsia, GERD and sinusitis. No serious adverse events have been reported so far [21, 22].

16.2.8.2 Gefapixant (AF-219)

Bladder distension releases ATP from the urothelium and ATP activates purinergic receptors such as P2X2 and P2X3. P2X3 purinoceptors are thought to play a role in sensitization of bladder afferent neurons in response to ATP, so that upregulation of ATP stimulation and P2X3 expression in the urothelium of patients with BPS may contribute to chronic symptoms. Gefapixant is a P2X3 receptor antagonist that has been investigated in a placebo-controlled, randomized phase II study (NCT01569438). The suggested dose is 50 mg BID–300 mg and common side effects are dysgeusia or hypogeusia. It improves urinary urgency and pain, but further investigations are needed [23].

16.2.8.3 Tanezumab

Tanezumab is a humanized antibody that blocks nerve growth factor (NGF) binding with high selectivity and specificity. It prevents NGF from interacting with its receptors on nociceptive receptors. In a phase II randomized double-blinded placebo-controlled trial, tanezumab showed a significant decrease in pain and urgency. The suggested dose was 200 μg/kg intravenous or 20 mg IV or 20 mg subcutaneous. Side effects included paraesthesia and headache [24]. It was also found that tanezumab improved pain in patients who had pelvic pain and a concomitant somatic syndrome, but not in patients with pelvic symptoms only [25]. This suggests that tanezumab may be helpful in patients with appropriate phenotypes.

16.2.8.4 Adalimumab

Adalimumab is a monoclonal antibody against TNFα, which is a proinflammatory cytokines release by immune cells. In a phase III randomized double placebo-controlled study, patients who received 80 mg subcutaneous loading dose followed by 40 mg every 2 weeks showed improvement in outcomes measures but no statistically significant difference between treatment and placebo group. Currently, adalimumab is not considered as a treatment option, but it might still have a role in ulcerative subtypes BPS [26].

16.2.9 Other Compounds

16.2.9.1 Quercetin

It is a bioflavonoid with a wide range of biological effects, including anti-inflammatory activity. The suggested dose is 500 mg BID. Further studies are needed to assess its efficacy [27].

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.9.2 Misoprostol

It is an oral prostaglandin analogue that is hypothesized to have cytoprotective effect on bladder. The suggested dose is 600 μg daily, but side effects are common and include abdominal cramping and diarrhoea [28].

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.9.3 L-Arginine

It is a semi-essential amino acid, precursor of nitric oxide (NO). NO may have immunoregulating properties and, taken systematically, L-arginine increases the production of NO. Current data does not support the use of L-arginine for BPS [29].

(Level of Evidence: 1. Grade of Recommendation: A)

16.2.9.4 Montelukast

It is a leukotriene receptor antagonist. Leukotrienes are produced by mast cells and may promote inflammation. In patients with BPS, montelukast at the dose of 10 mg daily can reduce frequency, nocturia and pain but the data supporting its use in BPS in not strong [30].

(Level of Evidence: 4. Grade of Recommendation: D)

16.2.9.5 Muscle Relaxants

There are insufficient data on the effectiveness of muscle relaxants in BPS.

16.2.9.6 Alpha-Blockers

Alpha-blockers are largely used in the treatment of BPH. They have moderate effect on total pain, voiding and QoL scores in BPS and their use may be considered in patients with a recently onset BPS [31, 32].

16.2.9.7 5-Aplha Reductase Inhibitors

As alpha-blockers, 5-α-reductase inhibitors are mostly used in the treatment of BPH due to their action on prostate volume. 5-α-Reductase inhibitors cannot be recommended for use in BPS in general, but symptom scores may be reduced in a restricted group of older men with an elevated PSA serum concentration [33].

16.2.9.8 Sildenafil

Sildenafil is a PDE-5 inhibitor mainly used for erectile dysfunction in men. Its mechanism of action is still unclear, but some hypothesis suggest that it can lower bladder smooth cells contraction sensibility, hence reducing potassium ions penetrating the submucosa and mast cell degeneration. Even though there is limited published data on its use, it seems that in patients with BPS sildenafil can improve objective and subjective parameters [34]. The suggested dose is 25 mg daily and most common side effects are flushing and headache.

16.2.9.9 Phytotherapy

Patients treated with phytotherapy have significantly lower pain scores. In particular, it seems that pollen extract administration significantly improves BPS patients' symptoms, while phytotherapy in general shows an overall favourable treatment response in BPS, especially on pain [35, 36].

16.3 Intravesical Therapies

Intravesical therapies can be used alone or in association with oral therapies and are indicated when first-line therapy fails. Its rationale is to replenish the deficient GAG layer or to modify the process of inflammation or hypersensitivity. These treatments have the main advantage to localize therapy into the bladder, thus reducing systemic absorption. Intravesical drugs can be used alone or in combination ("*bladder cocktails*").

16.3.1 Dimethyl-Sulphoxide

Dimethyl-sulphoxide (DMSO) is an organosulphur non-toxic solvent whose mechanism of action has not been clarified. However, it is thought to exert its clinical effect through several mechanism: it reduces inflammation and pain and facilitates detrusor relaxation [37, 38]. The instillation method has not been standardized, although generally 50 cc of a solution of medical grade 50% DMSO is instilled into the bladder. It can be given as a single-agent instillation or as part of bladder cocktail (see further). Side effects include temporary garlic-like odour and irritative symptoms. DMSO is listed in the AUA guidelines as a second-line treatment option; however the EAU guidelines state that there is insufficient data to recommend its use. Moreover, DMSO is the only intravesical agent approved for the treatment of BPS/IC by the FDA.

(Level of Evidence: 2. Grade of Recommendation: B)

16.3.2 Heparin

Heparin is a sulphonated GAG with the theoretical action of replenishing the urothelial GAG layer. It also has anti-inflammatory effects and inhibits fibroblast proliferations [39]. The suggested dose is 10′000–40′000 units and can be used alone or in association with other compounds, such as alkalinized lidocaine. Single-agent heparin studies have shown modest benefit in patients with BPS [40]. Side effects are not significant but may include local haemorrhage.

(Level of Evidence: 3. Grade of Recommendation: C)

16.3.3 Pentosan Polysulphate Sodium

Pentosan polysulphate sodium (PPS) in an oral heparinoid that likely exerts its effect by restoring the GAG layer; it also inhibits histamine release by mast cells and reduces the intracellular calcium ion level in the bladder [41]. At present, PPS is the

only oral agent approved by the FDA for the treatment of BPS. When taken orally, it achieves slow urine concentration resulting in a lag time before clinical improvement is observed. Intravesical therapy has the theoretical advantage of quickly achieving a response to PPS treatment. Intravesical PPS can be used in association with oral PPS resulting in a higher response rate than intravesical PPS alone [42].

(Level of Evidence: 4. Grade of Recommendation: D)

16.3.4 Lidocaine

Lidocaine is a local anaesthetic with rapid onset of action, more commonly used in combination with other agents. Alkalinisation helps the lidocaine to better penetrate the urothelium [43]. Lidocaine provides immediate response and no significant side effects are reported.

(Level of Evidence: 1. Grade of Recommendation: C)

16.3.5 Chondroitin Sulphate

Chondroitin sulphate (CS) is a component of the GAG layer which is deficient in patients with BPS. CS inhibits the recruitment of inflammatory cells to the deep layers of the bladder wall [44]. The suggested dose is 2% in buffered saline and no significant side effects were reported. CS is mostly used in association with hyaluronic acid (HA).CS is commercially available as Gepan® or Uracyst®.

(Level of Evidence: 1. Grade of Recommendation: C)

16.3.6 Hyaluronic Acid

Hyaluronic acid (HA) is another component of the urothelial GAG layer that has anti-inflammatory effects. HA is commercially available as Cystistat® that comes as a 40 mg dose in a 50 mL solution. HA-CS has been shown to reduce the production of pro-inflammatory cytokines, reduce urothelial permeability and facilitate the repair of the GAG layer [45]. HA-CS is commercially available as Ialuril®, a 50 mL preparation containing 1.6% HA and 2% CS with calcium chloride in water.

(Level of Evidence: 1. Grade of Recommendation: C)

16.3.7 Other Compounds

16.3.7.1 Oxybutynin

Oxybutynin is an anti-cholinergic drug mostly used in overactive bladder syndrome. When combined with bladder training, it provides significant urodynamics improvement but no effects on pain were reported [46].

(Level of Evidence: 4. Grade of Recommendation: D)

16.3.7.2 Triamcinolone

Triamcinolone is a corticosteroid that can be used as an intravesical instillation or administered via submucosal injection through cystoscopy. Low dose triamcinolone injection seems to be more effective in patients with Hunner's lesions [47]. More often, triamcinolone is used in combination with other compounds.

16.3.7.3 Bacillus Calmette-Guérin (BCG)

Bacillus Calmette-Guérin (BCG) is mostly used for vaccination against tuberculosis and in bladder cancer immunotherapy. There are insufficient data to recommend its use.

(Level of Evidence: 1. Grade of Recommendation: -A)

16.3.7.4 Vanilloids

Capsaicin and resiniferatoxin (RTX) are neurotoxins that specifically bind to the transient receptor potential vanilloid type 1 (TRPV1) which is involved in the development of bladder pain [48]. Despite their theoretical ability to alleviate bladder symptoms, vanilloids are currently not recommended [49].

(Level of Evidence: 1. Grade of Recommendation: -A)

16.3.7.5 Liposomal Sphingomyelin

Sphingomyelin is a phospholipid found in cell membranes. It is thought that its use in BPS could restore the GAG layer and decrease the cell permeability [50, 51].

16.3.7.6 Botulinum Toxin A (BTX-A)

Botulinum Toxin A (BTX-A) inhibits the release of acetylcholine and other neurotransmitters from both afferent and efferent nerve-terminals as well as ATP from urothelium [52]. Intradetrusor BTX-A injections provides reduction in pain and urgency compared to placebo [53, 54].

16.3.8 Bladder Cocktails

The intravesical intillation of a combination of more than one substance or drug is defined "bladder cockatail". Various cocktails have been described in the literature and most often they include anesthetics and/or coricosteroids in the preparation. These treatments can be administered at home in selected case. Below, we report some of the most used "bladder cocktails".

- 20 mL 0.5% bupivacaine, 20 mL 2% lidocaine jelly, 40 mg triamcinolone, 10–20,000 IU heparin, 80 mg gentamicin [55]
- 8 mL 2% lidocaine, 4 mL 8.4% $NaHCO_3$, 20,000 IU heparin [56]
- 50 mL 0.5% bupivacaine, 50 mL 8.4% $NaHCO_3$, 100 mg hydrocortisone, 10,000 IU heparin, 80 mg gentamicin [57]
- 50 mL DMSO, 44 mEq $NaHCO_3$ (1 ampule), 10 mg triamcinolone, 20,000 IU heparin [58]
- 300 mg PPS, 10 mL 2% lidocaine, 10 mL 4.2% $NaHCO_3$ [59]

– 40,000 IU heparin, 8 mL 1% (80 mg) or 2% lidocaine (160 mg), 3 mL 8.4% $NaHCO_3$ [60]
– 5 mL 4% lidocaine followed by 5 mL 8.4% $NaHCO_3$ [43].

16.4 Conclusion

The pharmacological therapy of BPS/IC is complex and requires a multidisciplinary approach. Although numerous studies on the use of several drugs in BPS are present in the literature, only few of them are appropriate and with adequate levels of evidence to provide them grades of recommendation. We believe that, as on one side we will learn more on the aetiological and pathophysiological mechanisms that lead to chronic bladder pain and IC, on the other side we will certainly develop more therapeutic opportunities for these painful conditions.

Currently, drugs in chronic bladder pain can be administered both orally and intravesically. We definitely believe that further efforts should be made to standardize the intravesical treatments, through several safe and efficacy experiences. Thus, in future, we might even be able to develop study protocols based on the patient's phenotype.

As BPS/IC population is heterogeneous and multiform, further studies are mandatory to better define the best therapeutic options in this setting, which should certainly be as patient's tailored as possible.

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Botulinum Toxin in Chronic Pelvic Pain Management

17

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17.1 Biology and Mechanisms of Botulinum Toxin in Alleviating Pain

Botulinum toxins (BTXs) are a large family of proteins produced by a gram-positive anaerobic bacterium, Clostridium botulinum. BTX was discovered in 1793 by a German physician and poet named Justinus Kerner [1], but identified only many years later by Emile van Ermengem, a professor of bacteriology [2] (Fig. 17.1).

Based on the use of neutralizing antibodies, botulinum toxin is currently classified into seven serotypes produced by different Clostridium botulinum strains: types A, D, C (C1 and C2), D, E, F, and G. To date, at least 40 different subtypes of BTX have been described.

The current nomenclature differentiates newly identified BTXs as novel subtypes based purely on an amino acid difference greater than 2.5% [3]. The neurotoxins are structurally similar but provided of serological and antigenic differences; types A, B, E, and (with a less extent) F cause human botulism, while types C and D are responsible for animal toxicity [4]. More recently, an eighth serotype (BTX-X) has been discovered but it has not yet been produced or characterized as a protein [5]. Of the seven serologic types of BTX (A–G), only two obtained FDA approval

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Fig. 17.1 Clostridium Botulinum. Scanning electron micrograph of Clostridium botulinum bacteria (rod-shaped). 386261 EYE OF SCIENCE/SCIENCE PHOTO LIBRARY

for clinical use: BTX-A (abobotulinumtoxin-A, incobotulinumtoxin-A and onabotulinumtoxin-A) and BTX-B (rimabotulinumtoxin-B). BTX-A, and particularly onabotulinumtoxin-A, are the most frequently used neurotoxins in clinical applications, due to an extensive research conducted for many years in different clinical fields. BTX-B (rimabotulinumtoxin-B) has only been approved to use for cervical dystonia [6].

17.2 Biologic Mechanisms of Botulinum Neurotoxins

The neurotoxins are initially biologically inactive until they underwent proteolytic cleavage into a 100-kDa heavy chain and a 50-kDa light chain [7] (Fig. 17.2).

The heavy chain is responsible for the toxin selectivity and irreversible binding to cholinergic receptors at the level of presynaptic motor neurons. However, the activity of the heavy chain is not limited to binding receptors at the neuromuscular junction but it is also able to bind to receptors at the level of autonomic ganglia, and post-ganglionic parasympathetic and sympathetic nerve endings. Once bound to the receptor, BTX is internalized and then separated allowing the light chain to move into the cytosol [8]. Here the toxin cleaves its substrate SNAP-25 (synaptosomal-associated protein of 25 kDa), a member of the SNARE (soluble N-ethyl-maleimide sensitive factor attachment protein receptor) complex, which is responsible for facilitating the fusion and release of acetylcholine. By binding to SNARE proteins (that include also VAMP-synaptobrevin and syntaxin), the toxin disrupts the ability of acetylcholine-filled vesicles from fusing at the terminal axon and thus not able to release the content. This results in flaccid paralysis [9]. Importantly, these effects are consistently achieved by a localized action after local delivery without systemic redistribution [10] (Fig. 17.3).

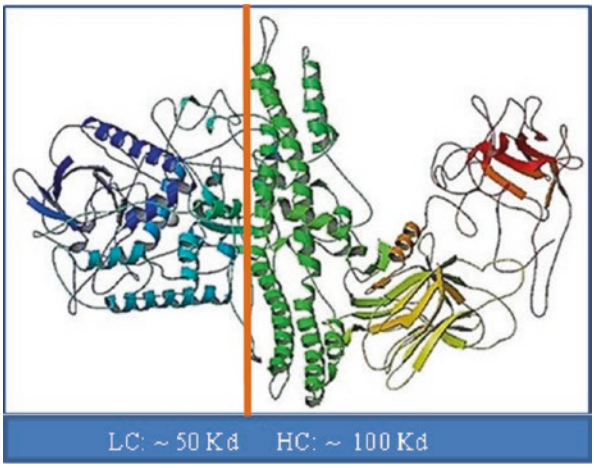

Fig. 17.2 Botulinum Toxin molecular configuration. *LC* Light chain, *HC* Heavy chain. Crystal structure image from the Protein databank doi: https://doi.org/10.2210/pdb3bta/pdb [7]

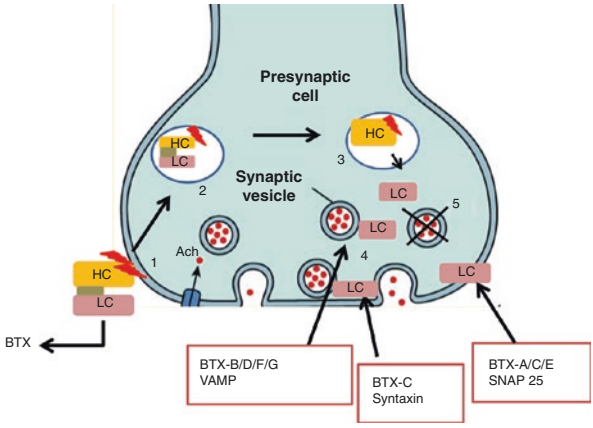

Fig. 17.3 Botulinum neurotoxin (BTX): the light chain (LC) is linked to the heavy chain (HC). The HC is functionally divided into the translocation domain which allows transport of the LC from the endosome into the cytosol, and the receptor binding domain. Once bound to the receptor (1), BTX is internalized and then separated allowing the light chain to move into the cytosol (2, 3). The LC of BTX/B/D/F/G specifically cleaves VAMP-synaptobrevin on the vesicle, (4) BTX/A/C/E cleaves SNAP-25 and BTX-C also cleaves syntaxin on plasma membranes (4), thus inhibiting the vesicular fusion and blocking the neurotransmitter (Ach) release (5)

17.3 Botulinum Toxins in Clinical Practice

Due to the abovementioned mechanism of action, BTX is currently used by local injection to treat several pathologic conditions involving skeletal muscles, smooth muscles, or exocrine glands.

In skeletal muscles, BTX is currently used to treat cervical dystonia, hemifacial spasm, blepharospasm, and spasticity in adult and children (on-label), and writer

cramp, tremors, and spasmodic dysphonia (off-label). In smooth muscles, the on-label use is related to neurogenic detrusor overactivity and idiopathic overactive bladder; indeed, an off-label use is currently applied in bladder pain syndrome and detrusor sphincter dyssynergia. With regard to exocrine gland application, BTX is used for exocrine glands hyperfunction (on-label sialorrhea, axillary hyperhidrosis; or, off-label, such as Frey's syndrome, plantar/palmar hyperhidrosis) [4], and also for aesthetic purposes [11].

17.4 Botulinum Toxins and Pain

More recently, BTX has also been used in pain-related disorders (on-label chronic migraine or off-label, such as osteoarthritis, neuropathic pain, and lower back pain). Although BTX was initially considered to alleviate pain through a simple muscle relaxation, thus providing decreased compression on local blood vessels and nerves [12], recent studies showed that the mechanism of action of BTX in pain relief is more complex. Indeed, in conditions involving intramuscular-administered BTX, relief in pain can precede and/or last longer in comparison to the muscle-relaxant effects, and this effect can be observed in distant areas from the injected site [13]. Independently from pain which might be related to increased muscle contraction, antinociceptive effect of BTX (particularly the neurotoxin A) has been described in different types of chronic pain not primarily associated with muscular hyperactivity, such as migraine and different types of neuropathic pain. One explanation may consist in the inhibition of the release of neurotransmitters involved in pain and inflammation at a peripheral level. Substance P, calcitonin gene related peptide (CGRP), glutamate, and transient receptor potential vanilloid 1 (TRPV1) have been demonstrated to be inhibited by BTX [4]. Substance P and CGRP are produced by neurons in the dorsal root ganglia and induce peripheral sensitization. The inhibition of the release of substance P and CGRP by BTX reduces tenderness and pain in sensitized areas. TRPV1 plays a role in the processing of peripheral thermal and inflammatory pain. While the anti-inflammatory effects of BTX seem to be dose dependent, the antinociceptive effects are not dose dependent. Conditions characterized by neuropathic pain, as post-herpetic neuralgia, diabetic neuropathy, post-traumatic neuralgia, phantom limb pain, trigeminal neuralgia, occipital neuralgia, and complex regional pain syndrome largely benefit from BTX treatment [4].

Another possible explanation for BTX-modulating pain is represented by its retrograde axonal transport to the central nervous system (CNS). It has been observed that, in addition to local uptake in the synaptic terminal, a distinct secondary uptake pathway results in retrograde transport of the fully active neurotoxin at distal sites [14, 15]. This retrograde axonal transport is followed by a process of cell-to-cell transfer (named trans-cytosis) by which the neurotoxin may gain access to second-order neurons in the CNS [16]. Both BTX-A and BTX-B may exert transynaptic effects following axonal transport [17], while BTX-E seems to be recruited for axonal trafficking in a significant less efficient manner. The long-range axonal transport of the neurotoxin from the site of uptake at the sensory neuron ending into the dorsal

root ganglion and CNS is believed to play a pivotal role for the activity of BTX in pain [16, 18]. In addition to neurons, BTX can impact the functional activity of glial cells, such as Schwann cells and astrocytes, which suggests the presence of yet another mechanism of pain modulation by BTX [19, 20]. Thus, the long-range transport along axons may be responsible for the displacement of peripheral injected BTX at the level of the spinal dorsal horn and brainstem, where it may exert the inhibition of the release of neurotransmitters/neuropeptides from nociceptive neurons in response to nerve damage [21].

New evidences have added some important concerns inside the mechanisms of action of BTX-A in modulating pain. c-Fos gene activation is a reliable marker of increased nociceptive transmission from primary afferents to second order sensory neurons. Activation of c-Fos can be initiated by the release of intrathecal SP through an action on NK1 receptors. This explains the possible BTX-A interaction with SP/NK1R transmission at the spinal level [22]. Moreover, activation of μ-opioid receptors is primarily known for its analgesic effect. While a direct molecular interaction between BTX-A and μ-opioid receptors has yet to be established, there are findings suggesting BTX-A modulates these receptors agonistically by an unknown mechanism [23]. It has also been observed that BTX-A restores the neuroimmune balance between pronociceptive (IL-1β and IL-18) and antinociceptive (IL-10 and IL-1RA) factors in the spinal cord of neuropathic rats. In experimental models, BTX-A downregulates pronociceptive interleukins IL-1β and IL-18 in the dorsal root ganglion and upregulates antinociceptive interleukins IL-1RA and IL-10 in the spinal cord [24]. Studies involving gene expression profiling and mass spectrometry suggest that chronic pain is associated with strong activation of certain neuronal genes, as well as genes associated with immune cell responses, including microglial activation. It has been observed that BTX-A not only attenuated neuropathic pain-related behaviors in rats by impeding injury activated neuronal function, but also reduced the activation of spinal microglia [25].

In CCI-exposed mice, BTX-A reduced the number of astrocytes, the percentage of active astrocytes, and the activation of microglia in neuropathic animals after chronic morphine treatment [26], and it modulated the immune response through a TLR2-dependent pathway in macrophages [27]. In synthesis, the supposed mechanisms of action of BTX-A in modulating pain are showed in Table 17.1.

17.5 Botulinum Toxins and Bladder Pain

Several laboratory studies and animal model researches have been conducted in previous years in the field of bladder pain/chronic pelvic pain. In an animal study, intravesical injection of BTX-A was able to inhibit ATP release from the bladder urothelium [28]. In a chronic spinal cord injury rat model, BTX-A injection was able to normalize alterations in ATP and nitric oxide (NO) release from bladder urothelium [29]. Other studies in rats demonstrated that BTX-A inhibited sensory neuropeptide release, including SP and CGRP, from isolated rat bladder preparations after cyclophosphamide-induced inflammation and in rat trigeminal ganglia

Table 17.1 Supposed mechanisms of action of Botulinum toxin type A (BTX-A) in modulating pain

Mechanisms of action of Botulinum toxin A in pain modulation
BTX-A could block nociceptor transduction, thus inducing a marked decrease in sensitivity of mechanical pain
BTX-A could reduce neurogenic inflammation and inhibits pain by preventing peripheral sensitization
BTX-A can inhibit primary sensory fibers promoting a reduction of peripheral sensitization, and an indirect reduction in central sensitization
BTX-A could decrease inflammation pain (II phase) by inhibiting the release of several neurotransmitters and neuropeptides including glutamate, substance P, and CGRP
BTX-A could reduce c-fos gene expression
BTX-A modulates the activity of μ-opioid receptors
This could be achieved either by:
– enhanced synthesis/release of opioid peptides
– enhanced opioid receptor function
BTX-A modulates cytokines expression and production
BTX-A regulates microglial and astroglial activity

cells [30], thus suggesting that the neurotoxin induces a potential clinical benefit in the treatment of neurogenic inflammation. Welch et al. found that BTX-A can inhibit the release of SP from cultured embryonic dorsal root ganglia neurons [31]. Injection of BTX-A in surgical wounds on an animal study in rats resulted in less infiltration of inflammatory cells than in the control group, with a lower transforming growth factor beta1 (TGF β1) expression in the BTX-A treated group [32]. This result suggested that BTX-A injection might control local tissue inflammation. Furthermore, BTX-A has been observed to inhibit cyclooxygenase-2 expression in a capsaicin-induced prostatitis rat model [33]. Other researches showed that BTX-A injection into the bladder can reduce urinary levels of nerve growth factor (NGF), by inhibiting the action of proinflammatory cytokines [34]. A reduction of NGF bladder tissue levels has been demonstrated also after BTX-A injections in humans [35]. In addition, BTX-A can inhibit the delivery of the transient receptor potential vanilloid 1 (TRPV1) to neuron cell membranes [36]. It has been observed that inhibition of P2X3 receptors on afferent terminals from BTX-A results in lower ATP release from the bladder urothelium and ameliorates pain in patients with bladder painful syndrome/interstitial cystitis [37]. P2X3-immunoreactive fibers have been found significantly decreased after BTX-A bladder injection also in humans affected by detrusor overactivity, and the reduction of P2X3 expression was significantly associated with reduction in urinary urgency and frequency [38]. Taken together, these results have posed the rationale to use BTX-A also in patients with IC/BPS.

17.6 Intravesical BTX-A in BPS/IC

Since 2004, pilot studies reporting the efficacy of BoNT-A for treating BPS/IC have shown controversial results. Smith et al. showed that the submucosal injection of BTX-A, 100–200 U into 20–30 sites inside the bladder, with a simultaneous hydrodistention, improved pain and urinary symptoms in 13 women affected by BPS/IC [37]. In these patients, Interstitial Cystitis Symptoms Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) questionnaires mean scores improved by 71% and 69%, respectively ($p < 0.05$), and daytime and nighttime urinary frequency and pain, as assessed by the visual analog scale (VAS), decreased by 44%, 45%, and 79%, respectively ($p < 0.01$). Symptoms relief appeared 5–7 days after treatment and lasted for a mean of 3.7 months. Giannantoni et al. reported the results of BTX-A intradetrusor injection in refractory BPS/IC patients [39]. In that study, 200 U of BTX-A was injected submucosally in the trigone and bladder floor under cystoscopy. Subjective improvement was detected in about 80% of patients at 1 month after treatment. Mean VAS scores and mean daytime and nighttime urinary frequency significantly improved as compared to baseline. More recently, further studies and randomized controlled trials appeared to better support the therapeutic effect of BTX-A in patients with BPS/IC. In a prospective study of Ramsay et al., 11 patients with BPS/IC received intravesical 200–300 U of BTX-A; an improvement in symptoms by 20% was detected 14 weeks after treatment [40]. In a one-year follow-up study, Giannantoni et al. reported significant improvements in VAS for pain scores and in urinary frequency in 86.6% of patients at both 1- and 3-month follow-up [41]. One year after treatment, pain recurred in all patients and dysuria was observed in nine cases. In a further study, the same authors used the Hamilton Anxiety Scale, the Hamilton Depression Scale, and the QoL SF-36 questionnaire to evaluate psychological function and QoL in 14 BPS/IC patients who received BTX-A intravesical injection [42]. At the 3-month follow-up, the majority of patients showed a significant improvement in anxiety, depression, and QoL [42]. A more recent randomized prospective study reported the results of BTX-A suburothelial injections in 67 patients affected by BPS/IC [43]. Patients were injected with 100 U BTX-A into 40 sites with a concomitant cystoscopic hydrodistention, or received hydrodistention alone. After 3 and 6 months from treatment, the ICSI and ICPI scores, VAS, frequency, nocturia, functional bladder capacity, cystometric bladder capacity, and global response assessment were significantly improved.

A prospective, randomized study investigated the effectiveness of BTX-A injections of different dosages, with a subsequent bladder hydrodistention, in comparison with bladder hydrodistention alone [44]. Two groups of patients underwent suburothelial injection with 200 U or 100 U of BTX-A, respectively, followed by cystoscopic hydrodistention 2 weeks later; another group of patients was submitted to cystoscopic hydrodistention without BTX-A injections. All patients remained under pentosan polysulfate intravesical treatment along the whole follow-up period. It was observed that intravesical injections of BTX-A followed by bladder hydrodistention was significantly more effective than hydrodistention alone with regard to

BPS/IC symptoms and VAS scores improvements. In addition, no significant difference was observed on the efficacy between different BTX-A doses although the adverse events were more common in the group treated with 200 U compared to 100 U group. In a recent prospective, randomized study, refractory BPS/IC patients received immediate injection or 1-month delayed injection of BTX-A while maintaining their actual treatments [45]. Responses rates were 73.5% at 1 month, 58.8% at 3 months, 38.2% at 6 months, and 20.6% at 12 months. Another multicenter, randomized, double-blind, placebo-controlled trial in 60 patients with IC/BPS refractory to conventional treatment also indicated that hydrodistention plus suburothelial injections of BoNT-A 100 IU can significantly improve the VAS score and increase cystometric bladder capacity at week 8 after treatment [46]. In another randomized, controlled study conducted in a small number of patients by Pinto and coworkers, BTX-A intravesical injections were compared with placebo (normal saline). Also in this case, the neurotoxin was superior as compared to placebo in inducing an amelioration in ICSI, ICPI, and VAS for pain [47]. In all the considered studies safety of BTX-A intradetrusor or sub-urothelial injection was good, and only in few cases increases in post-void urinary residual volume and urinary tract infections were detected after treatment.

17.7 BTX-A Transurothelial Delivery in the Treatment of BPS/IC

The ideal treatment modality to introduce BTX-A into the bladder should be represented by a needle-free delivery of the neurotoxin in order to induce a noninvasive bladder chemo-denervation [48]. Indeed, the current procedure is, although minimally, invasive and requires the use of cystoscopy and multiple injections into the bladder. This obviously poses the need to perform the injections under intravenous sedation or local anesthesia. In addition, avoiding the injection could allow to modulate only the afferent nerves localized into the submucosal space, with obvious therapeutic advantages. In overactive bladder (OAB), BTX-A has been administered together with dimethyl sulfoxide (DMSO), an organic solvent used to facilitate the delivery of several therapeutic agents into the bladder [48]. This co-administration has been provided to be useful in a clinical trial in women with refractory OAB [49]. Also protamine sulfate has been used in animals to enhance the uptake of BTX-A into the bladder wall [50]. Instillation of BTX-A has been performed with the co-administration of liposomes in a multi-center, placebo-controlled study including women affected by OAB [51]. As results, urinary frequency and urgency significantly improved but no urge urinary incontinence. The use of inert heat sensitive hydrogel preparations that increase the residence time of neurotoxin adjacent to the urothelium and allow for slow release exposure has been used to enhance the effectiveness of instilled BTX-A. OnabotulinumtoxinA embedded in the hydrogel TC-3 has shown efficacy in the treatment of OAB [52].

To date very few data exist on the use of BTX-A instillation with additional agents into the bladder in the treatment of BPS/IC. In a recent study, the use of thermosensitive hydrogel improved the intravesical delivery of BTX-A in 15 patients with IC/BPS [53].

17.8 BTX-A in the Treatment of Category III Nonbacterial Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

Among chronic pelvic pain syndromes, category III nonbacterial CP/CPPS is another clinical syndrome characterized by pelvic pain with or without voiding symptoms such as persistent urge to void and increased urinary frequency. Many similarities exist between IC/BPS and CP/CPPS, about epidemiology, etiology/pathophysiology, natural history, and response to similar treatments. Indeed, it has been recognized that IC/BPS and CP/CPPS are not organ-specific syndromes but urogenital manifestations of regional or systemic abnormalities, characterized by neuropathic pain (NP) [54]. In CP/CPPS, data about treatment with BTX-A are more limited as compared to those in BPS/IC. In addition, sites of administration and modalities vary largely, from injection of the neurotoxin into the prostatic gland to that into the perineal body and bulbospongiosus muscle. Indeed to date, only four randomized controlled studies have been published on the results of BTX-A administration in the treatment of patients affected by CP/CPPS [55–58]. The results of these studies are contradictory; in one study the response to treatment was defined as modest, although well tolerated [58], and in the other three studies the injection of the neurotoxin into the prostate gland obtained a reduction in pain, an amelioration in urinary symptoms and in QoL, as compared to placebo [55–57]. What is important to mention is the fact that the evaluated outcomes, the length of follow-up, the number of treated patients, and the reported side effects differ largely among the considered studies, and it is not possible to derive final conclusions from these results.

17.9 BTX-A in Vulvodynia and Vaginismus

Vulvodynia and vaginismus are clinical conditions in which treatment with the neurotoxin has been recently introduced. The effects of BTX-A in treating refractory vulvodynia and vaginismus to conventional therapies could rely on stretching, desensitization, and vessels dilatation of the injected sites, although to date no consensus exist on how and where the neurotoxin should be administered.

The first clinical study was published in 2004 and included 12 females with chronic pelvic pain and spasmus at the level of the levator ani muscle. In these women, treatment with BTX-A injections induced a significant improvement in pain [59]. In another open-label study including women affected by vulvar

vestibular syndrome and vaginismus, treatment with BTX-A injection was conducted along repeated injection cycles, and a consistent amelioration in pain was obtained along the whole follow-up period [60]. In a randomized controlled study of Abbott and coworkers, the neurotoxin was injected in pubococcygeus and puborectalis muscles of 60 women affected by chronic pelvic pain [61]. A not significant amelioration in VAS for pain and dyspareunia was obtained in the active group versus controls. In patients with vulvodynia treated with BTX-A injections, no statistically significant difference in cotton swab test, VAS, QoL, and Female Sexual Function Index questionnaire have been found when compared to placebo [62].

BTX-A injections have been performed under EMG guidance by Hedebo Hensen and coworkers, in 79 women affected by provoked vulvodynia, which was refractory to standard treatments [63]. The authors observed a not significant reduction in dyspareunia and improvement in QoL of treated patients. Overall, also in this field of application, there is the urgent need of randomized, controlled studies to really establish the efficacy and safety of BTX-A treatment.

17.10 Future Directions for BTXs in Treating Pain

To date there are many hypotheses under investigation in order to enhance the activity of BTXs in pain modulation. One possibility relies on protein engineering to exploit advantageous components of two BTXs in one synergistically active bio-therapeutic. An innovative approach could be to incorporate the desirable features from both BTX-A, which exhibits a longer duration of action, and BTX-E, which seems to be more active to modulate pain mechanisms, into a new composite toxin. To achieve this, in a recent study the most effective LC protease of BTX-E was attached to an enzymatically inactive protease of BTX-A (LC/A(H227Y), along with its translocation (HN) and binding (HC) domains in an attempt to deliver the BTX-E protease into sensory neurons having the longevity of BTX-A [64]. This creative approach successfully generated a novel protein LC/E-BTX-A with a mLD50 similar to that of BTX-E. This is probably the future direction by which a new neurotoxin will be successfully able to modulate chronic pain.

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Sacral Neuromodulation: To Improve Pelvic Pain or Associated Symptoms?

18

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Chapter Content

Chronic pelvic pain shares different gender-related clinical representations. The main association in males is with chronic prostatitis in the chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) according to the National Institutes of Health (NIH) prostatitis classification system [1]. Given the great number of symptoms belonging to different clinical domains, the phenotypic representation of CP/CPPS has been classified in the UPOINT clinical phenotypic classification system [2]. UPOINT is an acronym to underlie six clinical domains of symptoms: Urinary, Psychosocial, Organ specific, Infection, Neurologic, Tenderness of muscles. In women the association is with bladder pain (painful bladder syndrome, PBS), with interstitial cystitis (IC) and with endometriosis (END). The coexistence of PBS and endometriosis has been defined as the "evil twin syndrome" [3].

18.1 Possible Common Pathophysiological Processes in Both Genders

Chronic pelvic pain in males (CP/CPPS) and women (BPS/IC/END) share many clinical similarities and common neuropathophysiological processes [4]. About 30 years ago a neuromuscular dysfunction was suspected as underlying cause of symptoms in CP [5]. The hypothesis was an inappropriate spasm of the distal sphincteric unit, leading to increased pressure in the prostatic urethra with a resultant reflux of urine into the prostatic ducts [5]. The following inflammation was considered responsible for a further worsening of urethral spasm and, consequently,

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of voiding dysfunction. In women with obstructed voiding in Fowler's syndrome endometriosis was detected to have a higher incidence (29% vs. 6% in the control group) [6]. Obstructed voiding due to a failure in urethral sphincter relaxation during voiding is therefore a frequent dysfunction in females with endometriosis. The non-relaxing urethral sphincter in CPPS opened the way to the application of modulation of urethral dysfunction using sacral stimulation to obtain fatiguing of urethral sphincter. At the same time obstructed voiding with or without chronic pelvic pain in women became the main indication for sacral neuromodulation (SNM) in urinary retention, confirming the common neuropathophysiological process in both genders [7]. In a review Furuta et al. highlighted evidence of development of chronic pain through central sensitization [8]. The authors stated that nocisensors could also mediate an efferent signal through secretion of inflammatory agents in nociceptory sensory neurons. Peripheral inflammation would be responsible for peripheral sensitization. This phenomenon of neurogenic inflammation in chronic pelvic pain was analyzed in depth by Ursula Wesselmann in 2001 [9]. Neurogenic inflammation was identified at the origin of referred pain: neurogenic inflammation in the somatic referred zone triggered by inflammation of the bladder. Furthermore, a complexity of clinical manifestations are associated with pelvic pain in both genders. Functional bowel symptoms like constipation and obstructed defecation are common in men with CP/CPPS and women with PBS and endometriosis, the first often worsened by medical therapy, the latter due to non-relaxing pelvic floor. Associated symptoms of colonic inflammation testify cross-sensitization between the low urinary tract system and the colon.

Urgency/frequency are often associated with urge incontinence and hesitancy, dysuria and symptoms of voiding obstruction in both genders. The patients may often complain partial or complete urinary retention due to detrusor acontractility which correlates with somatic hypertone. A cohort of other symptoms may oppress the patients with CP/CPPS and PBS/CI/endometriosis. Diffuse joint pain, migraine, and depressive syndrome can in time become main symptoms.

18.2 Sacral Neuromodulation

Central and peripheral sensitization definitely opened the way to the application of SNM in chronic pelvic pain and voiding dysfunctions. Patients are selected based on the impact of main symptom on quality of life.

If a first stage SNM is performed, the effect of chronic stimulation may impact on the main symptom or on associated ones. Patients may report a significant improvement in pelvic pain with no impact of chronic stimulation on voiding dysfunctions as well as a good performance of voiding without any decrease in pelvic pain perception. What the patient perceives as main symptom, with important impact on quality of life, may not be modified by chronic stimulation. Whenever a first stage SNM is performed and the patient is evaluated by VAS for pelvic pain, voiding diary, Wexner scale, and bothersome associated symptoms reports, a lot of information are available. It is up to implanting group to help the patient make the

best choice whether to go further with SNM or stop the course towards permanent implant.

The efficacy of SNM is based on the theory that introducing exogenous electricity the native electrical signals of the nervous system change and alter the perception of what is in the periphery. SNM may change pain perception and associated symptoms through its impact along various reflex pathway: via the afferent nerves (in line with Melzack and Wall "gate theory"), by altering central processing of afferent signals or impacting at the efferent signals to the bladder and pelvic floor [4].

SNM does not treat the inciting cause of pain or bladder/bowel voiding dysfunction such as tissue inflammation or injury, but affects the neural circuitry mediating pain, the "pelvic cause of pain." The efficacy of SNM is based on the theory that introducing exogenous electricity the native electrical signals of the nervous system change and alter the perception of pain [4]. Not only the perception of pain is affected by chronic stimulation, but also associated symptoms that change their impact in patient's everyday life. The course of chronic first stage SNM may furthermore be affected by the use of association therapies (pharmacological and behavioral) that may potentiate the effect of exogenous electricity. If summation of afferent potentials from different triggers is possible, then association therapies for the control of the cohort of symptoms associated with pelvic pain might be an option.

18.3 Trying to Answer Initial Question

The chapter started with a question about the possible effect of SNM on pelvic pain or associated symptoms. We learnt from clinical practice that SNM may modify pain perception as well as bladder or bowel symptoms according to what reported from patient at follow-up. SNM impacts on neural circuitry modifying central perception. Follow-up of first stage SNM in a patient with CPP and associated urgency/frequency may highlight an unchanged VAS score but slight improvement in daytime frequency with significant increase of bladder capacity. In another patient chronic modulation may change the perception of pain without any impact on daytime frequency. The reason for these variable effects of chronic modulation is unclear, but it is up to implanting team to highlight a possible effect of chronic stimulation and discuss it with the patient to impact his/her perception of outcome.

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Treating the Pudendal Nerve: Infiltration, Radiofrequency, and Surgery

19

Ganio Ezio and Haitham Rbeihat

19.1 Introduction

The pelvis is innervated to a large extent by the pudendal nerve (PN) which is a mixed sensory, motor, and autonomic nerve. The pudendal nerve arises from the sacral plexus and is formed by the second, third, and fourth sacral nerve roots. The nerve exits through the greater sciatic foramen, crossing the ischial spine, between the sacrospinous and the sacrotuberous ligaments [1].

PN entrapment is a painful condition causing pudendal neuralgia (PNa) (also called Alcock's syndrome) that is frequently difficult to diagnose and is fundamentally a clinical finding. Most of the patients who suffer from this condition are female, one out of seven women affected by chronic pelvic pain [2], and it is most likely due to etiological factors common to the female sex, such as the long list of gynecological causes [3]. These patients have sought medical attention by visiting multiple doctors regularly complaining chronic pelvic pain, and are frequently offered multiple diagnoses and treatments without resolution of symptoms [4]. The diagnosis is often obscure leading to several modalities of treatment. The International Pudendal Neuropathy Association (TIPNA.org) evaluates the incidence of PNa to be 1:100,000, but, because it is often overlooked as a diagnosis, the incidence may be much higher [5]. There are multiple sites of pudendal nerve entrapment (PNE) and clinical presentation may be different.

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19.2 Clinical Presentation

A group of clinicians (the Nantes group) [6] set up in 2008 the diagnostic criteria for PN entrapment (PNE) (see below). Characteristic symptoms of PNa are pain in the anorectal region, perineum, labia, penis, or scrotum. Frequently PNa is unilateral.

The nature of pain has been usually described as sharp, burning, tearing, electrical, and stabbing, associated with the feelings of "a lump" in the vagina or rectum. Other associated symptoms involved are pain and straining with bowel movements, constipation, abnormal temperature sensations, dysuria, dyspareunia, and sexual dysfunction (including impotence, unpleasant arousal, or hypoesthesia). Voiding disturbances may also be present [7]. Patients may feel skin hyperesthesia (allodynia), so they avoid wearing clothes that may irritate the skin. Chronic vulvar and vaginal introitus burning pain (vulvodynia*)* might be a result of PNE [8].

19.3 Nantes Criteria for Pudendal Neuralgia

19.3.1 Essential Criteria

- Pain in the pudendal nerve territory.
- Pain predominately with sitting.
- Pain does not wake the patient at night.
- No objective sensory deficit on clinical exam.
- Pain relieved by diagnostic pudendal nerve block.

19.3.2 Additional Diagnostic Signs

- Burning, shooting, and stabbing pain; subjective numbness
- Allodynia
- Rectal or vaginal sensation of the presence of a foreign body
- Worsening of pain during the day
- Predominately unilateral pain
- Increased pain with defecation
- Exquisite tenderness on palpation of the ischial spine

19.3.3 Exclusion Criteria

- Exclusively coccygeal, gluteal, suprapubic, or hypogastric pain
- Exclusively paroxysmal pain
- Excessive pruritus
- Imaging abnormalities able to account for the pain

19.3.4 Associated Signs that Do Not Exclude the Diagnosis

- Buttock pain on sitting
- Referred "sciatic" pain
- Medial thigh pain
- Suprapubic pain
- Urinary frequency or pain on bladder distension
- Pain after ejaculation or erectile dysfunction
- Dyspareunia

19.4 Physical Exam

The physical exam findings in patients with pudendal entrapment may be subtle. Pain may be replicated with application of pressure on the pudendal nerve at the ischial spine or the inferior pubic ramus (percutaneously). The symptoms may worsen with passive internal and external rotation of the hip and resisted abduction/adduction of the hip flexed to 90°.

19.5 Anatomy of Pudendal Nerve (Table 19.1)

In 1836, Benjamin Alcock had studied the course of the internal pudendal artery [9–11]; thereafter a lot of remarkable descriptions of PN complexity and anatomic changeability have been made [9, 12–15]. The PN arise from the primary ventral roots of S2–S4 in the sacral plexus, forming one, two, or three trunks before its final branching [15, 16]; variable contributions from S1 and/or S5 [17–19] have also been described. The PN consists of 70% somatic fibers and 30% autonomic fibers. The visceral branch has 4–6 branches that connect with the

Table 19.1 Pudendal nerve anatomy

Origin	S1–S4 (mostly S2 and S3, rarely S4)
General route	From ventral piriformis through the greater sciatic foramen, over the ischial spine, through the lesser sciatic foramen, over the sacrospinous ligament, into Alcock's canal. Rectal branch comes off just before Alcock's canal and continues as perineal and dorsal nerve of the penis or clitoris
Sensory distribution	Anal, perineal, and genital sensation
Motor innervations	Anal and urethral sphincters, pelvic floor muscles
Anatomic variability	Sacral contributions vary; rectal nerve may separate outside the pudendal canal
Other relevant structures	Sacrospinous ligament, sacrotuberous ligament, and pudendal artery

roots of S2–S4 in order to form the pelvic sympathetic and parasympathetic plexus [19, 20].

The three terminal nerve branches of PN are the inferior rectal branch, the perineal branch, and the dorsal branch of the penis/clitoris. The perineal branch divides into the superficial and deep branches, and the former divides into the medial and posterotaleral of the scrotum/labia [21]. Interconnections between the perineal and rectal branches and the posterior femorocutaneous nerve are frequent [22].

The PN exits the pelvis through the greater sciatic foramen and proceeds caudally towards the piriformis muscle and the sciatic nerve. Then it re-enters the pelvis through the lesser sciatic foramen dorsal to the sacrospinous ligament and ventral to the sacrotuberous ligament [9, 15, 23–26]. The portion of PN in the interligamentous space is the most frequent site of entrapment. Immediately after the sacrospinous ligament, the nerve branches, giving off the inferior rectal nerve which penetrates the internal fascia of the obturator muscle to innervate its anal territory [27]. The perineal branch penetrates medially into the internal fascia of the obturator muscle, sliding towards the base of the urogenital diaphragm where it divides into its superficial and deep terminal branches. The dorsal branch of the penis/clitoris arises from Alcock's canal [12] and continues proximal to the inferior pubic ramus anteriorly; the area of Alcock's canal has also been described to be at risk for nerve entrapment.

The internal pudendal artery and vein are also found along the course of the pudendal nerve and its branches [15] which is important for nerve identification under Doppler ultrasonography [28–30]. At the gluteal level, the internal pudendal artery was found lateral to the nerves in 60% of cases, medial in 35% and on either side of the nerves (double), and slightly lateral and ventral in 5% of cases [26, 31–34].

19.6 Entrapment

There are several sites in which PN entrapment or compression can occur. Initially PNa was called "cycling syndrome" because the first identified etiology for its occurrence was cycling attributed mechanical compression of PN (Table 19.2) [11].

Other causes of PNa are direct injuries to the nerve during pelvic prolapse surgery using mesh and gynecological surgeries like hysterectomy and anterior colporrhaphy which could be explained theoretically by bleeding from the procedures into the Alcock's canal leading to scarring [35]. Traumatic falls on the buttock or back and vaginal delivery with or without instrumentation are also considered as part of PNa etiology from a mechanical point of view. Non-mechanical or biochemical causes of PNa are uncommon; they include viral infection (herpes zoster, HIV), diabetes, multiple sclerosis, and others [36, 37].

Table 19.2 Causes of pudendal neuralgia

1.	Pelvic surgery especially with use of mesh
2.	Pelvic trauma
3.	Childbirth
4.	Bicycle riding
5.	Prolonged sitting
6.	Constipation
7.	Anal intercourse/use of anal devices

19.7 Diagnosis of Pudendal Neuralgia

The diagnosis of PNa can be difficult; it is mostly clinical, depending mainly on taking properly the patient's medical history and performing a correct physical examination. Various tests are used to aid in diagnosis of PNa including diagnostic blocks of the pudendal nerve, pudendal nerve motor terminal latency (PNMTL), sensory threshold testing, Doppler ultrasound, and functional MRI. Diagnostic pudendal nerve block is important according to Nantes inclusion criteria and can be performed both unguided or with the use of electrical or image-guided techniques. Resolution of pain after the block, even if temporary, supports the diagnosis of pudendal neuralgia. These blocks may also have a very important therapeutic role. PNMTL measures conduction velocity of electrical impulses through the pudendal nerve [38, 39]. Electrical impulses are applied transvaginally or transrectally at the level of the ischial spine and the time needed to travel to the perineal muscles is measured. The simplest way to measure latency is by using a St Mark's electrode. Normal values are considered to be less than 3.5 ms in nulliparous patients but they are highly variable in patients with previous vaginal delivery or pelvic surgery due to pelvic floor muscle stretching; that is why most experts consider PNMTL to be inconsistent for diagnosis of PNa [40–42]. Quantitative sensory threshold testing is an important concept in diagnosis of PNa. The principle is that compressed nerves lose the ability to transmit the sensation of temperature changes and pressure [43, 44].

Pudendal nerves are positioned deep in the pelvis and only the terminal branches such as the dorsal nerve of the clitoris (penis) can be seen by high-frequency ultrasound; however Doppler ultrasound might be used in the interligamentous space to diagnose PNa because the nerve courses together with the pudendal artery and vein in a neurovascular bundle and it is hypothesized that compression of the nerve would lead to compression of the vein and so can detect a gradient in venous flow around the area of compression [45, 46].

Functional MRI detects tissues based on their biological properties rather than anatomical ones, so it can assess the nerve integrity by a method called "diffusion tensor imaging" which is based on the ability of water to diffuse more rapidly along nerve fibers rather than perpendicularly. But more researches are necessary to confirm its validity. Until now, there were no specific radiological findings in patients with pudendal nerve entrapment [47, 48].

19.8 Treatment of Pudendal Neuralgia

19.8.1 Conservative Therapy

Conservative therapy is considered as the core treatment for PNa. Avoiding certain exercises like cycling and adduction is important along with modification of lifestyle behavior and work environment that lead to minimize sitting and so decrease pressure on pudendal nerve. Usually the pain of PNa produce spasm in pelvic floor muscles which in turn add more pressure on the pudendal nerve causing an increase in levels of pain. This vicious circle seems difficult to break, leading to peripheral and central sensitization of pain. Nevertheless 20–30% of patients following lifestyle modification are predicted to improve [21]. If patients did not respond to lifestyle modifications, medications such as muscle relaxants, anticonvulsants, and analgesics can play a role in treatment. Most commonly used muscle relaxants are a twice-daily benzodiazepine, baclofen 4 mg vaginal or rectal suppository and tizanidine 2 mg twice a day. Gamma aminobutyric acid (GABA) analogs are used to treat neuropathic pain. Gabapentin (Neurontin®) and pregabalin (Lyrica®) act by binding to the α2δ subunit of voltage-dependent calcium channels in the central nervous system and stop the formation of new synapses and thus decrease neuropathic pain. Usually the starting dose for Neurontin is 300–900 mg/day in three divided doses, titrated up to maximum 3600 mg/day. Lyrica is usually started at 75 mg twice a day. Doses may be increased to a maximum of 600 mg/day in two to three divided doses [49, 50].

Osteopathic physical therapy is also applied in patients with pelvic floor muscular spasm, and it can rule out pudendal neuralgia if patients' symptoms improve after therapy. It includes manual techniques that help release muscle spasm and lengthen the muscle including myofascial release, soft and connective tissue mobilization, and trigger point release. Other treatments include ultrasonography, electrical stimulation, and biofeedback [51]. A good alternative treatment once there is no improvement in pelvic floor muscle spasm is Botulinum toxin injections into the pelvic floor with administered doses between 50 and 400 units of Botox® using a pudendal nerve block needle as reported in the literature [52].

Steroid injection to pudendal nerve is an imperative treatment for PNa through which local anesthetics (to block the nerve) and steroids (to minimize inflammation) are injected around the nerve and this can be performed image guided by fluoroscopy, ultrasound, or CT scan in both sexes, using electrical stimulation through the needle or unguided and transvaginal in women. Pudendal nerve perineural injections (PNPI) are usually achieved by infiltration of bupivacaine 0.25% 6 cc and corticosteroids around the pudendal nerves with two blocks between the sacrotuberous and sacrospinous ligaments and one block into Alcock's canal between the obturator muscle and its fascia. PNPI aims to relieve pain initially with bupivacaine which is of rapid onset, lasting hours to a few days. But for longer term effect corticosteroids are used with onset after 1–3 days, lasting 0–5 weeks. PNPI also relieves organ dysfunctions in which bladder symptoms may respond immediately but

typically more slowly than pain, while rectal symptoms will have slow recovery, though an immediate response may occur. Regarding sexual symptoms questions about nocturnal erections should be asked as a measure.

There are several techniques of PNPI for transgluteal and transvaginal approaches. Transgluteal technique can be guided by Fluoroscopy, CT, Ultrasound, or Electrical Stimulus. Patients with PNa noted that pain typically increases between weeks 3 and 4 after PNPI. PNPI can be repeated; it is found that the optimal time for PNPI treatment is at 4 weeks interval with series of three PNPI at weeks 0, 4, and 8.

Symptoms relief after PNPI may last hours, days, and weeks and they may completely resolve after one, two, or three PNPI. Failure of PNPI to relieve pain may occur in case of severe nerve compression, presence of concurrent Pain Generators like Maigne syndrome or posterior ramus syndrome, and injections into the ischioanal fat rather than the Alcock's canal [20, 38, 47]. Fannuci in a study conducted on 27 patients receiving PNPI for PNa stated that 24 h after treatment, 21 out of 27 patients reported significant pain relief. At follow-up at 3, 6, 9, and 12 months, 24 out of 27 patients reported >20% improvement in the Quality of Life (QOL) index [53]. In our experience, 66.3% out of on 169 patients responded well to PNPI; 20.5% had a long-term complete recovery, 79.5% had a positive temporary response.

Cryoneuroablation Freezing of the nerve can be performed intravaginally, at the ischial spine, at Alcock's canal, or at the individual branches of the pudendal nerve. This modality was described by Trescot and Prologo who found immediate improvement that last for 6 months [54, 55].

CT-guided pulsed dose radiofrequency (PDRF): A 20-gauge cannula is placed at the level of the pudendal nerve at Alcock's canal and the nerve is treated with 1200 pulses at high voltage (45 V) with 20 ms duration. In a study conducted by Masala et al. on 26 patients, treatment was successful in all patients. Mean VAS scores before PDRF was 9 ± 0.7. Patients had a great improvement in pain intensity after 1 week (mean VAS scores 3.8 ± 1.7, $p < 0.05$), with a stabilization of the symptoms in the following months (mean VAS scores 1.5 ± 1.1 at 6 months by PDRF, $p < 0.05$) and excellent results after 1 year by the procedure (mean VAS scores 1.9 ± 0.7, $p < 0.05$) [56]. PDRF was also used to treat the PN from a transvaginal approach in a modified lithotomic position; Rhames et al. identified the ischial spine and sacrospinous ligament transvaginally, and the nerve was pulsed at 42 °C for 120 s, with the patient noting 1.5 years of at least partial relief [57].

Surgical Treatment. Pudendal neurolysis surgery is usually considered after failure of the previously mentioned conservative therapies. The length, degree, and etiology of nerve injury usually affect the outcomes of pudendal nerve decompression surgery. Nearly 40% of patients who undergo decompression surgery have significant improvement in pain, 30% have some improvement, and 30% have no change in pain. However it is considered a successful surgery if there is at least a 50% reduction in pain and symptoms [58]. The four approaches are the transgluteal, the trans-ischiorectal fossa, the perineal, and the laparoscopic approach.

One of the most commonly used approach is the transgluteal one which was described by Roger Robert [38] in which a good visualization of the nerve is

achieved. The sacrotuberous and sacrospinous ligaments are divided to relieve compression on the nerve at the ischial spine. Alcock's canal is also explored to free the nerve from any tethered fascia. One of the advantages of transgluteal approach is that patient can retain pelvic stability and normal gait.

In the trans-ischiorectal fossa approach described by Bautrant [59], a small incision is made in the back of the vagina and the surgeon divides the sacrospinous ligament to release the compression between the ST and SS ligaments. Again Alcock's canal is explored by finger dissection and the nerve is released from any fascia that might be tethering it. Bautrant showed the response to 104 decompression surgeries, with 62% (53 out of 62 patients) of totally asymptomatic patients after 1 year.

The perineal approach was described by Shafik [8, 18]. In this technique (Anterior approach), the patient is in the lithotomy position, avertical para-anal incision 2 cm from anal orifice is made and the ischio-rectal fossa is entered across which the inferior rectal nerve is identified and hooked by finger and traced to PN in the pudendal canal where fasciotomy can be performed. This approach is totally blind using surgeon's finger and Shafik reported disappearance of pain in 9 out of 11 women.

Transperineal decompression can also be performed using a Balloon Probe which is introduced in the infrapiriformis area, then filled with 5 mL of saline solution. After that the balloon is narrowed and the probe is taken out. Thereafter the surgeon digitally locate the PN and completely release it by finger, thus making it a blind technique.

During the laparoscopic surgery, the sacrospinous ligament is divided allowing visual access of the nerve at the ischial spine and Alcock's canal. The nerve is freed from scarring, fibrotic tissue, and swollen varicose veins. A solution of heparin may be infused into the area to prevent scar tissue formation [5, 60].

We performed a total number of 43 transgluteal pudendal nerve decompression, we considered for surgery patients who met the Nantes' criteria with a positive pudendal block but persistent pain after injections. Seventy-two percent of the patients responded well; 13 had a complete recovery and 18 showed improvements >80% in a VAS scale. Twelve patients did not improve after surgery.

The outcome of surgical decompression of PN through the previously mentioned approaches is reviewed in literature.

Some postoperative problems might occur including transient neuropraxia which lasts days to weeks, urine retention which developed at first day in <1% of patients (usually males), and persistent postoperative pain which may require additional treatments in <10% of surgeries, physicians should be alert to concurrent peripheral neuropathies. Postoperative treatments usually begin after 4–5 months with the application of perineural injections of steroid and/or heparin, intravenous ketamine for spinal cord wind-up, and epidural anesthesia.

Other Therapies: Recently the injection of adipose tissue and stem cells into Alcock's canal of 15 women, a technique called "lipofilling," has been described. Two patients had no response, but there was an improvement in pain and in nerve conduction in the remaining patients [61].

19.9 Summary

Pudendal neuropathy is a tunnel syndrome. The resultant chronic pain can be treated nonoperatively and successfully in most patients with pelvic floor physiotherapy, medications, and treatment of associated problems, such as interstitial cystitis, endometriosis, bowel problems, and depression. If these approaches fail, symptoms may be related to entrapment of the pudendal nerve somewhere along its course, most frequently in the interligamentous space.

In order to locate the site of entrapment, the history of the trauma/symptoms, physical findings, and the results of nerve block are crucial. The exact role of the neurophysiologic studies and the newest radiologic imaging techniques is still vague even with the most powerful MR scanners, in identifying correctly the pudendal nerve branch compression sites, especially in people who have had previous surgery. Therefore, a decision can be made as to the most favorable surgical approach for a neurolysis of the pudendal nerve based on the patient's medical history and physical examination. Physicians need to take responsibility for all aspects of care, including recommendation for decompression surgery and psychological treatment. The PN may never heal in the presence of serious damage. Finally, significant postoperative care may be required and there is hope for relief of symptoms in almost 70% of people affected by pudendal neuropathy.

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Pelvic Physical Therapy and Rehabilitation

20

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20.1 Introduction

Over the years, associations related to various medical disciplines have proposed various definitions of chronic pelvic pain (CPP). The differences within the various definitions proposed concern not only the duration or precise location of the pain, but also other characteristics such as persistence or cyclicality, the sex of affected patients, the possible presence of associated symptoms and the possibility of identifying a triggering cause.

Currently, the studies have moved from the search for the triggering causes to the analysis of the factors that predispose to the pain and extend it once started. The main predisposing factors are of genetic [1] and cognitive-psychological [2] origin, while pathological changes in the nervous system cause maintenance of pain. Regardless of any peripheral damage, these changes may manifest clinically with impaired visceral levels and with the amplification of the perception of painful stimuli (hyperalgesia), up to the point where pain is felt even in the absence of a stimulus. The physical consequences are added to the repercussions of affective, cognitive and behavioural nature, which can contribute to the increase of symptoms.

On a diagnostic and therapeutic level there is no "*gold standard*". The diagnosis is often based on the exclusion of known pathologies, while many treatments have been proposed for the treatment, from alternative medicine to surgery, from physiotherapy to phytotherapy.

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Despite the variety of existing treatments, due to the lack of clarity of the aetiopathological mechanisms underlying CPP, the relative treatment is often unsatisfactory and limited to reduction of the symptoms. Currently, the increasing attention paid to the concomitant causes of CPP has been reflected in a new multimodal and multidisciplinary team approach. Within this team, an important role belongs to the physiotherapist, in fact various studies have shown that patients affected by CPP, compared to healthy controls, present altered parameters not only at the musculoskeletal level [3] but also at postural, respiratory and motor level [4, 5].

Furthermore, the clinical description of the various sub-categories of CPP seems to support the hypothesis according to which, independently of the causes at the origin of CPP, common signs may be present such as the presence of "*tenderness*" and "*trigger points*" *(TP)* of the pelvic muscles [6].

Although the presence of the physiotherapist is now commonly accepted within this therapeutic team, the scientific evidence supporting the effectiveness of physiotherapy is not yet clear [7].

20.2 Manual Treatment

People with chronic pelvic pain seek help from different medical specialists, in relation with a wide variety of symptoms: together with the pain related to the perineal area or more specifically to the anal area, to the coccyx, to the buttocks where the abdominal level may present symptoms such as dysuria, urinary urgency, frequency, hesitation and reduced flow power. Equally, patients may experience sexual disorders with difficulty reaching orgasm, stomach pain or during the sexual act, including erectile dysfunction for males and reduced lubrication in women. Gastrointestinal disorders, such as constipation or constant difficulty in evacuation, may also be present. For all these reasons patients can seek gynaecological urologists or surgical rectal orthopaedic neurologists, and often be referred to a specialist psychiatrist. In terms of rehabilitation, one of the most interesting points is the almost continual concurrence of painful muscle areas (TP), but also mucosal thinness at the point of pain and skin TP associated with pain, even secondary to previous visceral diseases.

The TP can be considered an outbreak of hyper-irritability within a muscle or within the band that causes pain; the pain manifests itself specifically for each muscle, and if the TP is active, it is always painful, reducing the stretching capacity of the muscle to direct compression, determining a local response ("twitch") and a pain related to distance.

This element, also well described and identified in the guidelines [6], allows for a primary role to be identified in the rehabilitation of chronic pelvic pain in manual treatment. Moreover, these clinical signs are essential in the rehabilitation of myofascial syndrome and fibromyalgia, clinical pictures where the presence of pelvic pain is frequently found.

In addition to the classic TP, the most common muscle problems are postural and biomechanical alterations, often secondary to muscle contractures in the context of the "non-relaxing pelvic floor" [8].

Concerning the pelvic-perineal muscles only, it is possible that the sign of hypertension is determined by "viscero-somatic" convergence [9], where the constant afferent nociceptive stimulation amplified by the phenomena of peripheral sensitization can determine, through an inter-neuronal system, an increase in basic muscle tone through activating the alpha-motoneurons.

Specularly, it has been shown that musculoskeletal dysfunctions in the pelvic region can cause biomechanical changes in the pelvic girdle and how shortening of the pelvic muscles can contribute to maintenance. It is a kind of neurogenic inflammation as demonstrated in animal models [5, 10].

Manual and myofascial component treatments are more effective than general massage [11], and still effective when used to treat trigger points in conjunction with painful bladder syndrome [12, 13].

However, to date it cannot be considered the only conservative approach that can be proposed though it is undoubtedly effective [7].

Among the different treatments proposed for inactivating the TP, manual therapy remains the first treatment option [14].

Soft tissue interventions described include different compression techniques [15, 16], massage [17], stretching [18], muscle energy techniques [19], strain-counterstrain [20], neuromuscular techniques [21] and positional release techniques [22].

The overall techniques applied directly, perpendicularly and vertically on sarcomeres can determine an action of rebalancing the altered length of the fibre and thus reduce pain [23]. Other authors hypothesize that effectiveness is linked to a spinal reflex induced by the manoeuvre, or linked to reactive hyperaemia caused by compression, potentially able to contribute to solving the trigger point issue [24].

In case of chronic pelvic pain, compression techniques have been applied with benefit to the piriformis muscle, gluteus maximus and levator ani muscles (pubovisceral, puborectal and iliococcygeal), as well as to the obturator internus [25].

Compression techniques can be associated with simultaneous stretching manoeuvres: they have proved useful when applied to the iliopsoas muscle and adductors in case of pelvic pain [26].

It is also possible to apply the transverse massage to the pelvic muscles, with a rhythmically exerted pressure perpendicular to the orientation of the muscular fibres. The treatment can last 10 min [27].

Among the neuromuscular techniques, the hold relax (HR) technique can be more easily applied: this is used to facilitate relaxation of the muscles in order to improve the amplitude of movement.

This method consists of an isometric contraction (absence of movement), setting a muscle in the stretching position (also called passive stretching) and holding the position for a few seconds. Subsequently, the muscle is made to contract, but with a resistance that does not allow for movement (isometric contraction). This lasts from 6 to 10 s.

By keeping the muscle in a stretching position, the contraction is stopped and then a stretching manoeuvre starts; this second stretch should reach a more advanced level than the first.

Again, in case of chronic pelvic pain, the technique can be applied with benefit to the piriformis muscle, gluteus maximus, iliopsoas and adductors.

Particular attention should be paid to compression and massage manoeuvres that can be performed through the anus or the vagina (if possible, as affected people are not allowed to be subjected to these manoeuvres) (Fig. 20.1) following the Stanford evaluation protocol and treatment [28].

Reference can also be made to the protocols proposed by Dejong or by Travell and Simons, subsequently modified by other authors [29–31].

All the protocols have the reduction of pain as the goal, through direct compression of the TP. The reduction of pain is achieved with a compression between 15 and 20 s, while the relaxation of the muscle area in which the TP is located is obtained with a minute's compression, then followed by a stretching of the area itself, moving the finger parallel to the direction of the muscle fibres for an amplitude of about 2 cm, repeating the gesture 4–5 times. These stretching movements aim to lengthen the shortened muscle areas and must be carried out correctly for each individual muscle in the context of which there is a TP.

This type of protocol can also be applied to muscles that can be treated from the outside, by the skin; however it is absolutely appropriate, after an adequate clinical evaluation, to perform the manoeuvres also by the endocavitary route, primarily on the different components of the elevator muscles of the anus, on the internal obturator and the piriformis [32].

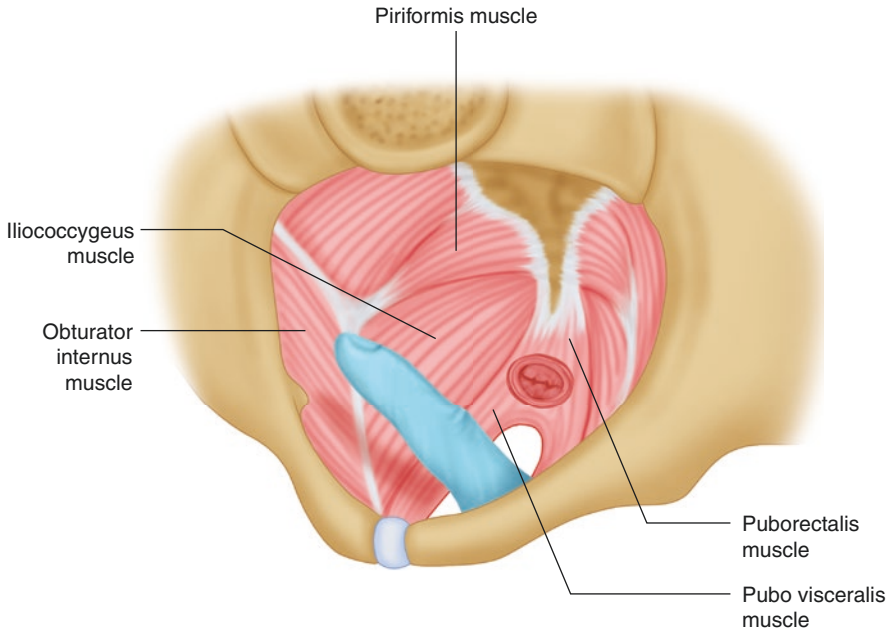

Fig. 20.1 Pelvic floor release trigger points

Since it is not easy to find trained and skilled physiotherapists in the required techniques, self-treatment has been proposed utilizing a personal therapeutic wand to inactivate trigger points (Fig. 20.2) [25].

Finally, it is necessary to integrate segment treatment with a more global treatment with particular attention to posture and possible alterations of the respiratory pattern. The evidence of the close relationship between the respiratory diaphragm and the pelvic diaphragm are now consolidated, both in physiology and pathology, and confirmed by the increased frequency of respiratory disorders in the presence of pelvic-perineal dysfunctions [33, 34].

Connections between the stability of the sacroiliac joint and the respiratory and pelvic dynamics have also been observed, particularly in women: in the presence of perineal dysfunctions, the static of the spine (in particular with the hypertonicity of the external oblique and a more frequent "flat-back" posture) would also be altered, with a further secondary impairment of the pelvic floor muscles [35].

Home exercises are also crucial for maintaining the results obtained thanks to rehabilitation: the "Sniff, Flop and Drop" technique [36] aims to maintain coordination between the respiratory diaphragm, abdominal wall and pelvic floor. The patient, supine, is instructed to Sniff in through the nose, keeping the chest down and allowing the lower stomach to fill up or Flop. The patients flop or swells out on the in-breath into the palpating hand without forcing, bracing or using the upper abdomen to push out. The patient simultaneously Drops the chest down as the diaphragm descends, and expect to feel a connection to the pelvic floor as it too lets go.

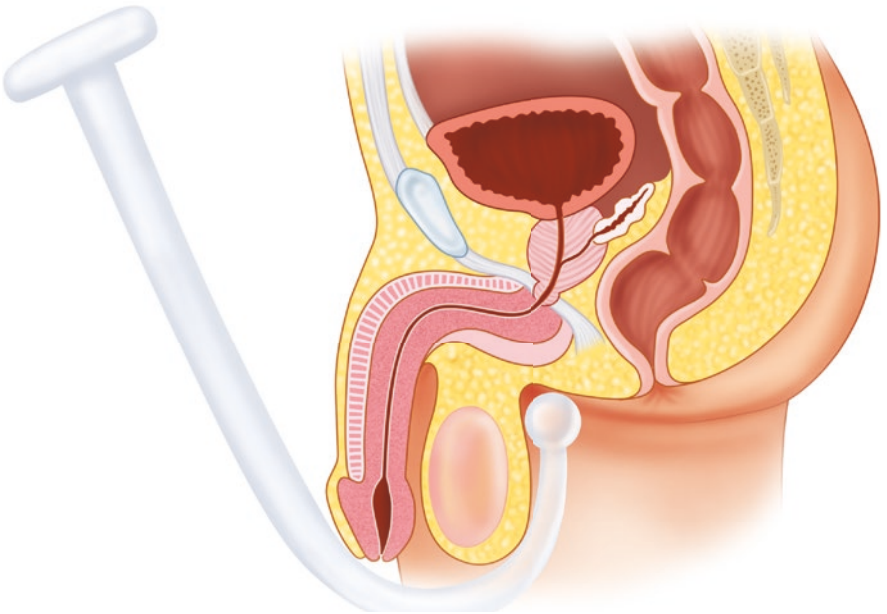

Fig. 20.2 Personal massage wand to inactivate external trigger points

20.3 Biofeedback

The use of behavioural techniques for the treatment of chronic pelvic pain has been in the literature for many years and, beyond the evidence under the diagnostic aspect [37], there are no controlled studies that confirm its usefulness in adults and the developmental age [38–40].

The key element of the technique is the chance to recognize the muscle tone of the pelvic floor, thanks to surface electromyography (sEMG) with an endocavitary probe and, making the electromyographic data available in graphic form on-screen, the chance for the person to recognize and manage the tension levels in his muscles. The most commonly used protocol provides that the patient, through voluntary engagement, is also able to achieve relaxation, thus improving not only the basic tone, but optimizing the function of the pelvic floor itself through the alternation of contraction/relaxation.

The Glazer sEMG assessment protocol is performed by alternating voluntary contractions and resting phases, and it takes approximately 10 min:

1. One minute pre-baseline rest
2. Five rapid phasic contractions, with 10 s rest between each
3. Five 10 s holding tonic contractions
4. A single 60 s holding endurance contraction
5. One minute post-baseline rest

After the training (a home program of two 20 min sessions per day with contractions of the pelvic muscles as hard as possible in supine, sitting and standing position), the sEMG changes demonstrate a reduction of the discharge of muscular fibres type 2 [41].

20.4 Transcutaneous Antalgic Electro-Stimulation

The acronym TENS (Transcutaneous Electrical Nerve Stimulation) is conventionally attributed to analgesic treatment by transcutaneous electro-stimulation.

For decades, electrical current, administered through transcutaneous electrodes, has been used for therapeutic purposes, and electrical stimulation can be considered a real possibility for treating pain of various kinds.

The theory of “gate control” [42] is based on the existence of different types of nerve fibres responsible for transmitting “sensations” from the periphery to the central nervous system of the human body. It is the basis of the construction criteria for modern electro-physiotherapeutic equipment.

As a result, there is:

Small Diameter fibres of myelinated type A∂ and unmyelinated type C. They are attributed with the property of “leading” the “pain” signal from the peripheral algic

zone to the control system, which transmits it from the spinal cord to the cortical nerve centres for recognition and modulation (below 2 m/s).

Large Diameter fibres of myelinated type Aβ; these are attributed the "conduction" of "tactile" sensations. They have a much higher conduction speed (around 70 m/s).

If we succeed in stimulating the large diameter fibres without affecting the others, the inhibition of the small-diameter fibres is activated at the spinal cord level, and therefore a sort of blockage of the "pain route" towards the brain (ascending route).

The selective stimulation of large diameter fibres is made possible by the difference in sensitivity (conduction velocity) between them and small diameter fibres. Therefore, the width of the stimulation pulses will play a decisive role in the field of electro-stimulation.

Basically: C fibres are unexceptionable with pulses of less than 200 μs, A∂ fibres are unexceptionable at stimuli lasting less than 10 μs, and Aβ fibres remain exceptionable even with pulses of only 2 μs.

The theory of "gate-control" has been the subject of criticism and subsequent reconfirmation by several authors. The fact is that, even if the mechanism of control remains unknown, even if it is doubtful whether it is a pre- or post-synaptic inhibition, even if the role of the gelatinous substance is not known, it cannot be questioned that the mechanism of "gate control" exists, even if its functional role and the details of its mechanism have yet to be defined.

Of course, the "gate control" theory is not the only theory: a more recent interpretation suggests a mechanism based on the stimulated production of endorphins. These, although with different biochemical mechanisms, act on the system of descending pain control, causing a high analgesic effect. For the stimulation of the production of endorphins, the same criteria of width discrimination in impulses do not apply.

As we have seen, the antalgic action of electro-stimulation is attributable to different mechanisms, depending on the intensity and duration of the pulses:

Short pulses and at moderate intensity will only affect large-diameter fibres (more sensitive and at higher conduction speeds). The immediate and short-term analgesic action derives from a "block" of pain at the level of the posterior horns of the spinal cord.

Longer pulses and with higher intensity simultaneously stimulate "painful" fibres; therefore their antalgic action is not attributable to the mechanism of gate control, but to the reflex stimulation of the central system responsible for the production of morphine-like substances (endorphin-encephalines).

The stimulation frequency would also play an essential role in effectiveness, but there are still many differences of opinion: the low frequencies (around 10 Hz.) would produce an antalgic action that would be later and less intense yet more lasting, while frequencies above 50 Hz would result in faster but short-lived analgesia.

In the case of perineal electro-stimulation, using a vaginal or anal probe, usually a type of probe is chosen to convey the impulses at the point of most significant

pain. TENS has been validated for CPP, and treatment—with daily application—is usually continued for at least 3 months [43].

20.5 Percutaneous Tibial Nerve Stimulation

Percutaneous tibial nerve stimulation (PTNS) is a neuromodulation technique for treating symptoms of the lower urinary tract, obtained by electrical stimulation of the posterior tibial nerve.

The mechanism of action is still unclear [44], but it is assumed that PTNS modulates the signals arriving and departing from the bladder (S2-S3) with afferent and efferent stimulation, through the sacral plexus; there are probably also central type paths for which stimulation is not only afferent retrograde, but there would be a plastic reorganization of the cortical network triggered by peripheral neuromodulation [45].

The posterior tibial nerve is in close association with the rear tibial artery and is a mixed nerve containing motor and sensory fibres, which originates from the L4-S3 nerve roots; these same roots innervate the detrusor, the urinary sphincter and all the pelvic floor muscles.

The patient is placed in the supine position for the stimulation procedure with the knees abducted and bent and the hips in external rotation (frog position); the introduction of a 34 gauge needle is planned approximately 4–5 cm cranially to the medial malleolus. The point where the needle is introduced was already known by traditional Chinese medicine [46], the SP6 point, as the point for bladder regulation and to relieve pelvic symptoms. A recent study by Yang et al. [47] however would have shown how the stimulation of the BL33 point (very close to S3) is equally effective in inhibiting the overactive bladder.

After positioning the needle, an electrode is placed on the ipsilateral heel bone. The needle is connected to a stimulator of about 9 V. The generator that delivers the electrical impulse has fixed stimulation parameters: 200 μs pulse range, 20 Hz pulse frequency and variable stimulus intensity between 0.5 and 9 mA, respecting the patient's tolerance threshold. To confirm the correct positioning of the needle, the power of the stimulus is slowly increased until the bending of the big toe and/or the waving of the other fingers is obtained. Furthermore, patients report a sensitive response to stimulation, such as tingling in the soles of the feet or fingers [48]. The commonly used protocol involves a session per week lasting about 30 min for 10–12 weeks; in this regard, there are studies in the literature that show the same effectiveness, in less time, for more frequent applications [49, 50]. The results seem to depend on the number of stimulations performed but not on time elapsed since the start of the stimulation programme.

PTNS is effective for chronic pelvic pain [51, 52] and a systematic review provides evidence that PTNS is a safe intervention and about the efficacy of PTNS on pain, and Quality of Life measures of CPP [53].

20.6 Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique, with the aim of creating electric fields within the cerebral cortex due to the application on the scalp of electrodes delivering a continuous low current; in particular, the application to the motor cortex can modulate cortical excitability [54].

For CPP, rationale for motor cortex stimulation (anodal stimulation (1 mA of direct current for 20 min) placed on the primary motor cortex, C3 or C4 according to the 10/20 EEG international system) has excitatory effects, and can change thalamic activity [55]. The cathode (inhibitory effects) is placed over the contralateral supraorbital area.

In recent years, tDCS has been used in the study of chronic pelvic pain, including in combination with transcutaneous electrical nerve stimulation (TENS) [56], and it was shown that it could be a promising tool to reduce chronic pelvic pain [57]. Its use, however, must today be confirmed by larger randomized controlled trials.

20.7 Conclusions

Although clinical practice and existing guidelines attribute an essential role to the physiotherapist in the management of chronic pelvic pain, currently the studies present in the literature regarding the effectiveness of rehabilitation treatment are scarce (10 RCTs) and present numerous critical points in the methodological approach, mainly because of the difficulty in making therapists and patients blind.

Current innovations in the classification and distribution of chronic pelvic pain syndromes allow the drafting of more specifically sectoral algorithms. The diagnostic-therapeutic algorithms may, therefore, in the near future, have a specific path based on the sector of the pelvis "involved" and make not only the diagnostic framework easier but also the therapeutic effect better. There is no doubt that the earliness of the diagnosis and its correctness are essential prerequisites for therapeutic success which, although it may not always be global, improves the patient's quality of life while preserving the organ function as much as possible. This result is utopian if the patient is not framed within a path (pain team) in which the multidisciplinary aspect allows each of the players (medical specialists, nurses, midwives, rehabilitation therapists) to have a precise role at a precise moment in the treatment and, above all, follow-up. There is no doubt that scientific progress in each of the medical disciplines that contribute to defining the clinical picture and the aetiology of chronic pelvic pain will bring improvements also from a physiotherapy point of view, for this reason further investigations in this sense are desirable.

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The Multidisciplinarity in Chronic Pelvic Pain Management

21

Marco Soligo

Chronic pelvic pain (CPP) is a multidimensional condition currently defined by the International Continence Society as "persistent pain lasting longer than 6 months or recurrent episodes of abdominal or pelvic pain, hypersensitivity or discomfort often associated with elimination changes, and sexual dysfunction often in the absence of organic etiology" [1].

This definition represents a consensus around the evolution of understanding about a clinically challenging condition. The concept of being a dysfunctional pain is clearly expressed. The substantial nonorganic nature of CPP has to be interpreted in the light of the pain–time relationship: after 6 months persistence of pain even a possibly causative organic lesion is very difficult to be defined. Characteristics of pain at that point may involve a neuroinflammatory process, with central sensitization and the deployment of complex mechanisms of pain control. This implies a possible modification over time of the patient pain perception in terms of topography, intensity, duration, and recurrence [2].

Therefore the pain–time relationship, modulated by a subjective predisposition and/or psychosocial unfavorable conditions, has the power to amplify the original stimuli and increase complexity of mechanisms involved in pain control, thus transforming the clinical picture from a single organ issue to a multidimensional one.

In fact, even though the diagnosis is commonly initially proposed by organ specialists after having excluded an organ-specific involvement, the management of a CPP condition by a single organ specialist is frustrating both for the caregiver and for the patient.

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It is nowadays well established that a multidisciplinary assessment and multimodal treatment represents the highest quality of pain care, and this is particularly true in CPP.

In 1992, Flor et al. confirmed with a meta-analytic review that multidisciplinary treatments for chronic pain are superior to no treatment, waiting list, as well as single-discipline treatments such as medical treatment or physical therapy, with stable effects over time. Noticeably they also remark improvements extended to behavioral variables such as return to work or use of the healthcare system [3].

In the last 20 years the value of a multidisciplinary approach to chronic pain in general and specifically to CPP has been constantly confirmed [1–4].

Many reasons can be advocated to support a multidisciplinary approach in CPP.

From an epidemiological point of view in many cases pain involve more than one pelvic area. CPP is less frequently reported in male as prevalence data on prostate pain syndrome (PPS) are limited and confounded by other conditions and bladder pain syndrome (BPS) shows a female predominance of about 10:1 [5]. In a UK primary care survey an annual prevalence of CPP of 38.3/1000 was observed. In women 31% of the diagnoses were primarily gynecologic in origin. However in half of cases pelvic pain was not isolated, but associated with irritable bowel syndrome in 24% of cases, overactive bladder syndrome in 9% of cases, and all three symptoms were associated in 15% of cases [6, 7]. Therefore urologic, gynecologic, and gastrointestinal expertise might be required and these are the most commonly involved professionals, at least at a starting point.

From a pathophysiological perspective most recent understanding on pain mechanisms have widened the spectrum of professionals potentially involved from urologists, gynecologists, and colorectal surgeons or gastroenterologists to physicians specializing in physical medicine and rehabilitation, neurology, anesthesiology, rheumatology, psychiatry, sleep medicine, and addictions. That being the case other team members, a part from medical staff, are key elements in the management of CPP: nursing, physiotherapy, occupational therapy, kinesiology, clinical nutrition, psychology, pharmacy, and social work.

It is more than evident that CPP represents a complex condition. Management has to be tailored accordingly: a single treatment approach has limited chances of success, at least in the long term, while a multimodal treatment model, potentially with concomitant actions, has a higher probability of success. This implies moving from a simple treatment approach to a concept of treatment strategies. Targeting the biological pain generators with medical, surgical, and rehabilitative interventions need to be supported by a variety of psychosocial and rehabilitation strategies directed toward improved coping, appropriate lifestyle changes, physical fitness, and fitness for work.

Single professional skills and expertise are traditionally considered a guarantee for a successful treatment in many conditions. But the possibility of delivering high standard level of care relies on multiple medical and also non-medical aspects even within the context of one single discipline. Therefore, the higher the complexity of the clinical condition, the more organizational and logistical aspects play a significant role on the final result of patient management. CPP represents one of the

medical contexts where organizational aspects are so important. In this light the role of professionals dedicated to the coordination of different activities of a multidisciplinary CPP clinic is pivotal to achieve healthcare needs efficiently and effectively. The professional figure of Clinical Case Coordinator should be considered in any multidisciplinary organizational model. Specific interprofessional education programs are needed to implement this professional role [8].

Despite the great emphasis on multidisciplinary approach in all guidelines on chronic pain management [1–5], very few paper strictly investigate critical points in multidisciplinary services.

In 2001, Bondegaard Thomsen et al. evaluated the available evidence on the economic effectiveness of multidisciplinary pain treatment of chronic nonmalignant pain patients. They critically emphasized the lack of knowledge when evaluating multidisciplinary pain treatment, not only in respect of the principles of economic evaluations. In their review authors noticed serious methodological problems in study designs and choice of outcome measures, making impossible to give an answer to whether multidisciplinary pain management in chronic pain patients is cost-effective or not [9].

Outcome measurement represents a key factor, and really the last decade has been one of tremendous growth in the area of Patients Reported Outcomes (PROs), with influences from scientific and regulatory communities; this is well documented in the most recent update of the International Consultation on Incontinence (2017). Despite this, the lack of robust PRO tracking systems (i.e., electronic PRO software) still represent a major limitation for comprehensive assessment of multidisciplinary pain services [10].

A process toward services improvement in specialty pain medicine practices is of outmost importance, as there is a dearth of reports on quality improvement (QI) initiatives. Heres et al. (2019) in a brief research report on this subject well documented the possibility to improve the standard of care. In this study a fee-for-performance model coupled with peer review assessment significantly incentivized the process of comprehensive pain assessment and multidisciplinary treatment planning ($p < 0.01$ for the change in rate of compliance) [11].

Once more the key element is represented by the accountability of clinical outcomes. Future research should focus on developing strategies to implement the measurement of relevant clinical outcomes, and this is particularly necessary in the multidisciplinary approach to the CPP.

Within this context the concept of improving clinical performance, while paying attention to the system sustainability, has a lot to do with the *value in healthcare*, defined by Michael E. Porter in 2010 as "*health outcomes achieved per dollar spent*". In Porter's view *value (outcomes/costs)* must be the parameter capable to unify the interests of all actors in the health system: patients, payers, providers, and suppliers. Value encompasses efficiency: "Cost reduction without regard to the outcomes achieved is dangerous and self-defeating, leading to false "savings" and potentially limiting effective care [12]."

The compelling debate around the concept of value in healthcare is still ongoing with the U.S.A. Institute of Medicine defining *high value clinical care* (HVC) as "the

best care for the patient, with the optimal result for the circumstances, delivered at the right price" [13]. Deborah Korenstein in her 2015 JAMA Editorial notices: "This definition encapsulates the essence of being a good doctor, emphasizing the fundamental importance of the patient perspective and the importance of cost, in the sense that the best care is delivered as economically as possible. It is clearly the desired destination, but the context of HVC must be understood to know how to get there [14]."

It is out of the focus of the present chapter to go further into this debate, but, as far as we are concerned, it is relevant to understand what is moving around us and the crucial role of outcomes measurements and strategies to measure them.

Clinicians should be aware of the possible margin of improvement in the management of CPP, particularly when a multidisciplinary, multimodal approach is considered.

Efficiency in Chronic Pain Clinic has been recently scrutinized by Hundley et al. (2019) applying a specifically dedicated diagram (Gnatt diagram) at a single outpatient multidisciplinary pain management clinic in a university teaching hospital. The authors collected data from 81 patients on five clinic days investigating time tracking data for each phase of clinic visit and pain-related diagnoses. Currently 30-min interval are allotted for new patients and 15 min for each follow-up visit. The time spent by the patient in the clinic was subdivided into *total waiting time* and *total service time*, being the last one intended as total time an advanced practice provider, resident, fellow, and/or attending physician spent with the patient in the examination room and/or procedure room. What is remarkable in this paper is that *total service time* in a multidisciplinary clinic dealing with pain from different body areas differed dramatically ($P = 0.0051$) based on the diagnosis, with chronic abdominal or pelvic pain scoring the highest service time.

This further confirms the complexity of pelvic pain, requiring an extra time for clinical management. In the study, as an average, service time for new patients was of 24 min (IQR, 17–31 min) and it was 16 min (IQR, 11–23 min) for established patients. However abdominal and/or pelvic pain and facial pain consistently had service times exceeding the 15-min allocation for return visits. Apart from the practical fallout of suggesting to adopt clinical diagnosis as a criteria for scheduling consultation time allotment, this observation has a more general relevance, as inaccurate time allotment for patients can affect not only patient satisfaction but also the overall quality of care [15].

In conclusion, CPP is one of the most demanding area of pain management. A multidisciplinary, multimodal approach represents the highest quality of care and is increasingly being considered the standard of care in this field. Delivering a multidisciplinary service is not simply a matter to offer a summation of different discipline expertise; it requires an actual integration between them and with different behavioral and social aspects. To accomplish with this organizational aspects is crucial and the key professional figure of Clinical Case Coordinator has to be promoted. To move steps ahead clinicians and caregivers in general have to become familiar with PRO and outcomes measurement instruments. Value in healthcare represents one of the most interesting challenge in the future. CPP multidisciplinary services are in the frontline to depict this future.

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