

INTERNATIONAL PAINFUL BLADDER FOUNDATION



Interstitial Cystitis/ Bladder Pain Syndrome

**Interstitial Cystitis, Bladder Pain Syndrome,
Hypersensitive Bladder, Hunner Lesion Disease
Chronic Pelvic Pain, Associated Disorders**

An overview of Diagnosis & Treatment

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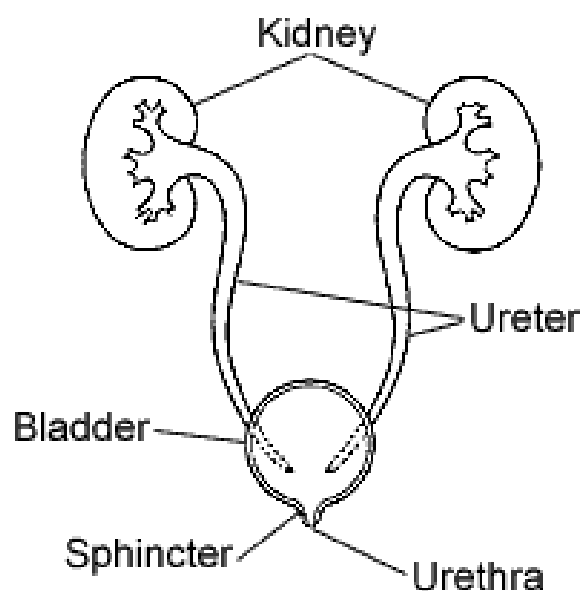
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TERMINOLOGY AND ABBREVIATIONS USED:

- Interstitial Cystitis: IC
- Bladder Pain Syndrome: BPS
- Painful Bladder Syndrome: PBS
- Hypersensitive Bladder: HSB
- Chronic Pelvic Pain: CPP
- Chronic Pelvic Pain Syndrome: CPPS
- Chronic non-bacterial Prostatitis/Chronic Pelvic Pain Syndrome: CP/CPSP
- Chronic Overlapping Pain Conditions: COPCs
- Urologic Chronic Pelvic Pain Syndrome: UCPPS
- Hunner Lesion: (formerly Hunner's ulcer or Ulcerative IC) also known as Classic IC or Hunner Disease or Hunner IC (HIC)
- Associated Disorders also known as Comorbidities or Non-Bladder Conditions
- Ketamine Cystitis: KC, also known as Ketamine Associated Cystitis



CHAPTER 1 - WHAT IS INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS)?

A normal urinary bladder should not cause pain or hypersensitivity. Pain, irritation, discomfort or a feeling of pressure in and around the bladder, with a frequent and often urgent need to urinate can have many different causes. It may be related to the urinary tract, the genital tract, the bowel, nervous system or muscular system. It may be due, for example, to bacterial, viral or fungal infections, infestations, stones, benign or malignant tumours, endometriosis, inflammatory systemic autoimmune disease, drugs or chemicals including in recent years ketamine abuse. Table 1 on page 20 provides a summary of many possible causes of these symptoms (so-called confusable diseases).

However, if a thorough investigation has revealed none of these disorders, there is another possibility. Interstitial cystitis/bladder pain syndrome (IC/BPS), also known as painful bladder syndrome (PBS) or - particularly in East Asian countries - as hypersensitive bladder (HSB) and sometimes grouped under the collective heading of chronic pelvic pain (CPP), is a distressing, chronic bladder disorder of unknown cause, with persistent or recurrent symptoms of pain/hypersensitivity, irritation, discomfort or pressure sensation related to the bladder and usually accompanied by a frequent and urgent, overwhelming need to urinate day and night even when there is very little urine in the bladder. While the symptoms may resemble a urinary tract infection (cystitis), tests show no infection in the urine and reveal no other disorder that could account for the symptoms.

Currently two main types: with or without lesions

At the present time, two main types can be distinguished:

- **the classic inflammatory type with Hunner lesion (formerly known as Hunner's ulcer or Ulcerative IC, sometimes also referred to today as Classic IC, Hunner Disease or Hunner IC)**
- **the non-lesion type**

While symptoms may be similar, cystoscopic findings are different for these two types and the approach to treatment is also different. Further information is given under Chapter 4 Diagnosis and Chapter 5 Treatment.

Current research into subtyping (or *phenotyping*) may lead to the identification of more subtypes in both of these categories.

What are the symptoms?

The characteristic symptoms of IC/BPS are:

- **pain/hypersensitivity, irritation, pressure, discomfort or other unpleasant sensation related to the urinary bladder,**
- **a more frequent need than normal to urinate (*frequency*) both day and night and/or**
- **an urgent, overwhelming need to urinate (*urgency*) due to increasing pain or unpleasant sensation.**

- *Pain, hypersensitivity, irritation, pressure, discomfort or other unpleasant sensation that may worsen as the bladder fills; urinating often alleviates the pain and may give a temporary sense of relief;*
- *Suprapubic pain or discomfort, pelvic pain (lower abdominal pain), sometimes extending to the lower part of the back, the groin and thighs;*
- *In women there may be pain in the vagina and vulva;*
- *In men, pain in the penis, testicles, scrotum and perineum;*
- *Both men and women may have pain in the urethra and rectum;*
- *Pain with sexual intercourse in both men and women (dyspareunia); pain on ejaculation in men;*
- *Pain may worsen or be triggered by specific foods or drinks or even medication;*
- *A frequent need to urinate (frequency), including at night (night-time frequency);*
- *An often overwhelming, urgent need to urinate (urgency).*

The pain or hypersensitivity may be experienced as discomfort, tenderness, irritation, burning or other unpleasant sensation in the bladder, or in the form of stabbing pain in or around the bladder, even in the vagina, or may simply be a feeling of pressure on or in the bladder or a feeling of fullness even when there is only a very little urine in the bladder. In many patients, the pain is relieved temporarily by urination, while some patients may also feel pain or burning following urination. The pain or discomfort may be constant or intermittent. It may also be felt throughout the pelvic floor, including the lower bowel system and rectum. In some patients the pain may be very severe and debilitating. Other patients may have frequency with/without urgency and without a sensation of true pain. What they may experience, however, is a feeling of heaviness, fullness, discomfort or pressure or simply an irritated sensation in the bladder. Sexual pain with intercourse is a typical feature in both men and women.

Urinary frequency means that a person needs to urinate more frequently than normal during the daytime and at night. However, this will also partly depend on how much a patient drinks, on the climate where the patient lives, how much the person perspires and on medication the patient may be taking which could have a diuretic effect. In IC/BPS, frequency may sometimes be very severe with some patients needing to urinate 60 times a day or more, but frequency is generally seen as being anything over approximately 8 times a day. However, this figure of 8 voids a day should only be seen as an approximation since the number of voids per day depends on the individual's way of life and environment.

Frequency is by no means always related to bladder size. While some patients may have a type of IC/BPS with a shrunken bladder with a scarred, stiff wall and a small capacity under anaesthesia, other IC/BPS patients with a normal-sized bladder may nevertheless have severe frequency due to hypersensitivity on filling. A typical feature of IC/BPS is the need to empty the bladder several or multiple times during the night. The amount of urine passed may be small, even just a few drops.

While a voiding diary can be useful to show frequency and the volume of urine passed, frequency can vary from day to day and week to week, depending on whether the patient's symptoms are flaring or relatively calm.

Urinary urgency in IC/BPS is an overwhelming, urgent need to empty the bladder due to increasing pain or discomfort or other unpleasant sensation that becomes impossible to tolerate any longer and may in some patients be accompanied by a feeling of malaise and/or nausea and stress sensation. Some patients find that having to postpone urination leads to retention or difficulty in getting the flow started. The nature and cause(s) of this urgency sensation in IC/BPS patients are still not fully understood but might be due to a leaky bladder lining that permits toxic elements from the urine to penetrate the bladder wall.

The painful urgency of IC/BPS (also known as sensory urgency) is completely different from the sudden urgency in overactive bladder with urgency incontinence and the two should not be confused.

Who gets IC/BPS? Men, women and children, of all ages, worldwide!

As diagnosed at the present time, IC/BPS is mainly found in **women**. Approximately 10-20% of IC/BPS patients are **men** who may in the past have been incorrectly diagnosed as having non-bacterial prostatitis (inflammation of the prostate gland) or prostatodynia (pain in the prostate gland). A complicating factor is that chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), also known as prostate pain syndrome, is clinically very similar to IC/BPS and the two conditions have many overlapping symptoms. However, this possibility of misdiagnosis in men may mean that more men may in fact have IC/BPS than hitherto thought and the percentage of male patients with IC/BPS may

therefore be higher. A diagnosis of IC/BPS should be considered in men who have pain perceived to be related to the bladder. However, both CP/CPPS and IC/BPS can occur together!

IC/BPS is also found in **children**. However, since in the past the old NIDDK IC research criteria excluded children from studies, many doctors consequently thought that IC did not occur in children. There has therefore been relatively little research or scientific literature on IC/BPS in children in the past two decades and some doctors are still hesitant to give a diagnosis of IC/BPS in a child. It can, nevertheless, occur in children of any age. Many adults with IC/BPS report that they had urinary symptoms in childhood or adolescence and needed to go to the toilet more frequently than their peers.

IC/BPS is found in **all countries around the world** and in all races. However, prevalence figures vary enormously from study to study and country to country and depend on what criteria and definitions have been used for diagnosis and what diagnostic methods have been used to reach the diagnosis. Furthermore, many prevalence figures have tended to bundle all patients with a painful, hypersensitive bladder together, without making any distinction between lesion/non-lesion types. The unfortunate result is that nobody can say with any degree of certainty at the present time how many people may have IC/BPS, while in some countries IC/BPS is considered to be a rare disease but in others not.

At present, the only distinction usually made is between the so-called Classic IC with Hunner lesions and the non-Hunner lesion type. A relatively smaller percentage of patients (estimates vary from 10-50%) have Hunner lesions (*Note: the old term was Hunner's ulcer but this was a misnomer since these are not usually true ulcers. They are today described as lesions*). However, while this Hunner type interstitial cystitis used to be considered rare, it is now believed that it may be more common than originally thought but simply not getting diagnosed.

Many researchers now believe that the classic type with Hunner lesions and the non-lesion type may be two different diseases. Further information on this is provided in Chapter 4 on Diagnosis. While some patients may have an inflammatory type of bladder condition, others may not and here too there may be further subtypes or phenotypes.

How does IC/BPS start?

The symptoms may begin for no apparent reason, or sometimes following surgery, for example in the case of women following a hysterectomy or other gynaecological or pelvic operation, after childbirth or following a bacterial infection of the bladder or repeated infections. Onset may be very slow, building up over many years or it may be sudden and severe. Some patients recall having bladder problems in childhood or adolescence, needing to go to the toilet more frequently than others, long before they developed pain.

In the very early stages of the disease or in a mild form of IC/BPS, the symptoms may only occur in attacks known as "flares". This leads many patients and their doctors to think that it may be an infection (bacterial cystitis). If the patient fails to respond to antibiotic treatment, it is important for a urine culture to be carried out (not just dipsticks) in order to be absolutely sure that bacterial infection can be excluded.

However, the fact that a patient has IC/BPS does not mean that the patient never develops urinary tract infections (UTIs) in addition to their IC/BPS. An infection in a hypersensitive IC/BPS bladder can considerably exacerbate the IC/BPS symptoms, further irritating the already painful or irritated bladder. In this situation, following confirmation of an infection, the IC/BPS patient should indeed be treated with a suitable antibiotic to clear up the infection.

But the symptoms of IC/BPS do not go away, they persist or keep on returning. In some patients, the symptoms may gradually worsen, but this greatly varies from patient to patient and is not necessarily

the case. The symptoms of IC/BPS patients without Hunner lesions may increase very slowly over a period of many years or remain stable and unchanged or even go into remission, while others (with Hunner lesion) may progress from an early stage to an advanced stage with a shrunken, scarred, stiff bladder wall (fibrotic bladder) and small bladder capacity in a shorter space of time.

It should be emphasized, however, that **many patients never progress further than a relatively mild form of IC/BPS** and that many patients have a normal bladder capacity under anaesthesia. There is currently no evidence to show that patients with non-lesion IC/BPS later go on to develop the lesion type. These may indeed be two separate diseases of the bladder, although the symptoms may be similar. Future research should shed light on this.

Exacerbation and remission

Spontaneous flares and remission are a characteristic feature of IC/BPS in many patients. Many women find that their symptoms are exacerbated just before or during menstruation, during ovulation or if they are taking contraceptive pills. Women may also find that their symptoms temporarily increase while going through the menopause. Any kind of stress, whether physical or psychological, for example rushing around trying to do too much, can trigger a flare. Many patients also find that a flare can be triggered by certain foods and drinks and even certain medications or vitamin supplements, resulting in irritation of the bladder.

Cause

Despite considerable research into many different aspects of IC/BPS, the cause is still unknown. The many theories have included an increase in mast cell activity, an abnormality in the bladder lining (GAG layer) causing leakage of toxic elements in the urine through to the underlying layers, neurological (C-fiber upregulation, central pain sensitisation), autoimmunity, allergy/hypersensitivity, occult infection (still being studied) and many more hypotheses. Some researchers have explored the possibility of heredity or genetics playing a role since IC/BPS may occur in more than one person in the same family (mother and daughter or two sisters).

A contemporary way of viewing IC/BPS is within the framework of chronic (pelvic) pain syndromes. Research in recent years has indicated that abnormal nerve activity may be a key factor in the chronic aspect of pain in IC/BPS and the way the pain appears to spread throughout the pelvic floor. At least a subset of patients suffers from one or more non-bladder pain syndromes in addition to IC/BPS and this is currently being looked at by researchers within the NIDDK Multidisciplinary Approach to the study of the Pelvic Pain disorders (MAPP Network project) in the United States. Current research is looking at chronic pain and central sensitisation or cross-sensitisation from one organ to another.

Numerous theories, no answers.

In summary, there are numerous different theories and much research has been carried out, but no real answers have so far been found. No-one yet knows what causes IC/BPS and whether it could in fact be a collection of different bladder disorders with similar symptoms. It is still an enigma!

IC/BPS can cause great stress and anxiety

Although many patients may experience a temporary worsening of their IC/BPS symptoms as a result of physical or psychological stress, it is particularly important to emphasize that IC/BPS is not a psychosomatic illness. The pain/discomfort, frequent and urgent need to urinate day and night and consequent lack of proper sleep experienced by IC/BPS patients, together with the impact of the disease on every aspect of the patient's life may themselves be a significant cause of stress, anxiety, sleep disorders, exhaustion and depression.

CHAPTER 2 - IMPACT ON LIFE

The IC/BPS patient not only has to cope with the bladder disease itself and all its symptoms, but also the consequences of this disease on his/her life in the widest sense. IC/BPS can have a major impact on the social, psychological, occupational, domestic, physical and sexual life of the patient and affect a patient's quality of life and the very structure of their life and their relationships with their family, partner and others. Learning how to cope is an important part of treatment.

Where am I going to find the next toilet?

The frequent and urgent need to urinate can form an obstacle to work, travel, visiting friends, or simply going shopping. When outside the confines of their home, the IC/BPS patient's life is dominated by the question "where am I going to find the next toilet?" Before every outing, the patient will carefully plan a network of toilets, known by patients as "toilet-mapping". Many patients say: "If I don't think I will be able to find a toilet, I simply don't go out". This kind of situation can make a patient uncertain and afraid to leave the safety of their home. Indeed, there are sadly many patients who tell us that they almost never go out. And let us not forget the patients in less developed countries where there may be no public toilet facilities at all.

Social isolation

The social consequences of IC/BPS should not be underestimated and may force a patient to adopt a completely different lifestyle. Through embarrassment that they need to use the toilet so frequently, patients may no longer visit even their family and friends. It's difficult for them to go out to a cinema or theatre or even just for a walk in the park. Their social life may be non-existent and they may feel – and in fact be – totally isolated from the world around them.

Some jobs are impossible with IC/BPS – financial impact

The frequent need to urinate may make it difficult for some patients to carry on working or they may be forced to change to a different type of job that allows them the possibility of easy, frequent access to toilets. Work in some jobs becomes impossible when you need to keep running to the toilet, are suffering from fatigue or drowsy from pain medication. The impact of IC/BPS on their work and career may mean missed workdays, unemployment and cause patients and their family considerable financial loss. This situation is far worse if the patient has no official diagnosis and consequently no access to social benefits or medical treatment.

The fact that many treatments – particularly bladder instillations – are not reimbursed in many countries also creates great financial hardship.

Physical and psychological impact of sleep deprivation and disruption

In addition to this, the pain and the frequent, urgent need to urinate make patients stressed and exhausted from lack of sleep. Some severe patients need to urinate 40-60 times a day and may sleep no more than 20 minutes at a time at night. Sleep deprivation or disruption can have a detrimental impact on people. Without proper sleep, a person deteriorates both physically and psychologically. This too can make some types of work and everyday activities impossible and even hazardous. See Chapter 7 on Fatigue in IC/BPS patients.

Emotional impact, depression and frustration

From a patient perspective, the very fact that they have a disease for which there is no known cure makes many patients very depressed and frustrated. Patients may feel anger that it took so long to diagnose, that so many doctors may have told them that, because they couldn't find anything wrong, it must be all in the mind, stress, psychological... Patients may increasingly feel that nobody in the medical profession believes them. Although on the one hand, the patients know they have these very real symptoms, they may start to lose their confidence, question their own sanity and feel a sense of

uncertainty, anxiety, helplessness, panic attacks, while depression can cause complete inertia, closing them off from the world, a situation that is often not helped by family and friends who say that if the doctor claims nothing is wrong, the doctor must be right. In this period of non-diagnosis, a patient may lose all faith in the medical system and feel rejected by this system. The lack of proper sleep makes sufferers continually tired. They may have problems tolerating treatment and may feel sedated and confused by pain medication. Patients long to be able to turn the clock back to when they were normal and find it difficult to look ahead or make plans for the future.

Still taboo and stigmatized

Bladder problems are still taboo in today's world and make sufferers feel stigmatized and isolated from their friends. The fact that the disease affects the bladder and means that patients keep looking for toilets makes them (and everyone else around them) constantly embarrassed.

Impact on family life and relationships

IC/BPS has an impact on the entire family from many points of view. It alters the patient's relationships with both partner and children because the bladder condition makes it difficult to act like a normal parent or a normal partner. IC/BPS patients are tired and irritable from lack of proper sleep, from coping with the pain and from the constant trips to the bathroom. The inability to cope, to look after the family, to do normal things with partner and children may create a feeling of guilt.

Patients may also be so anxious about when the next unpredictable flare is going to occur that they try to do too much at home for the family or at work and thereby actually induce a flare, creating a vicious circle. Other patients may suffer from persistent unrelenting pain that makes them continually exhausted.

Family members don't understand IC/BPS at all because they can't see anything wrong on the outside. So, unless they are very understanding, they may become resentful at the impact on their lives. If available, family counselling may help family members to understand the problems of the patient and to help the patient to solve the needs of the family in a low-stress way.

Sexual relations

IC/BPS can have a big impact on sexual relationships since sexual intercourse may be painful for both male and female patients. For some women, it may be totally impossible because the urethra, bladder, vagina and vulva are too painful. Anatomically, in women the bladder and vagina are close to each other and this can lead to pain or irritation during penetrative intercourse. In the case of men, ejaculation may cause them intense pain.

This is an aspect of the impact of IC/BPS on a patient's quality of life which is of very great importance. Sex is a normal part of the lives of human beings. If this form of intimacy is taken away, cracks may begin to appear in a relationship about which a patient may be very concerned and feel deeply guilty. Communication between the partners is essential. It is important for patients to be able to discuss this problem with their partner and for them to try to find solutions together, if necessary with the help of a sexologist/sex therapist or relationship counselling with sex education. Patients themselves may find it difficult or impossible to raise this intimate and embarrassing subject with their doctor. It is therefore important for the care provider to raise this issue.

Optimal pain treatment can also help the problem of painful sex in female patients. (However, it should be noted that use of painkillers such as NSAIDs may lead to erectile dysfunction in men!). Tips for sexual intercourse include: a warm bath to relax the pelvic muscles, urination before and after sex, thorough cleanliness by both partners to prevent infection, use of non-irritating lubricants, pre-medication such as painkillers 20 minutes before sex, engagement in foreplay to limit thrusting time,

different positions to reduce pain and symptoms, and thinking of creative ways of sex without vaginal penetration (“outercourse”) so as to maintain some level of sexual intimacy.

Patient support groups

Patients and their families need to be well-informed about IC/BPS, its diagnosis, treatment and coping strategies. Patient support groups can play an important role not only in providing this kind of information but also in providing emotional support. Patient-to-patient counselling is invaluable since only another patient truly understands what IC/BPS symptoms are actually like and their impact on life. Contact with other patients can be a great relief and a big step forward in learning how to cope.

While there is currently far greater awareness of interstitial cystitis/bladder pain syndrome around the world today and many more patients are now receiving a diagnosis, there are nevertheless still countries where knowledge of this disease scarcely exists.

CHAPTER 3 - BRIEF HISTORICAL OVERVIEW

“Previous to the latter half of the nineteenth century but little was known about diseases of the urinary apparatus in women. And while the relatively more urgent and dangerous diseases of the male organs had exacted the closest attention, the modesty of women, as well as the inaccessible nature of the affections, conspired to hinder an earlier scientific investigation of their genito-urinary organs.” (Howard Kelly, *Operative Gynecology*, 1912)

In 1808, Philip Syng Physick, a renowned surgeon from Philadelphia, was reported as describing a painful inflammatory bladder disorder with an “ulcer in the neck of the bladder”, producing the same symptoms as stone (a common cause of bladder pain at that time). In 1836, the Philadelphian surgeon Joseph Parrish described the condition as "tic douloureux" of the bladder, a term commonly used for trigeminal neuralgia, which he attributed to his mentor Philip Syng Physick. He wrote: “I have known instances of great suffering in the urinary organs, from this form of disease”.

In the same year in France, Louis Mercier wrote about unusual and perplexing perforation of the bladder from “ulcers” in males for which he could find no cause, there being no stone, no venereal history and no sign of tuberculosis.

The earliest record of the term interstitial cystitis discovered so far can be found in *A Practical Treatise on the Diseases, Injuries and Malformations of the Urinary Bladder, the Prostate Gland and the Urethra* by Samuel D. Gross, Professor of Surgery in Philadelphia, 3rd Edition revised and edited by his son Samuel W. Gross and published in 1876. In the section Diseases of the Urinary Organs, Part I, Chapter I (Inflammation of the bladder and its results), he writes: *“When all the coats are implicated, it is termed interstitial, or parenchymatous cystitis...”*

Two years later, in 1878, the term interstitial cystitis appeared again in the first edition of a book on diseases of the female urethra and bladder in which Alexander J.C. Skene, a gynaecologist from Brooklyn, described a bladder condition characterized by inflammation. “When the disease has destroyed the mucous membrane partly or wholly and extended to the muscular parietes, we have what is known as interstitial cystitis”, wrote Skene.

This was echoed by Van Buren and Keyes in 1880 who explained:

“Inflammation of the bladder, according to the anatomical portion of its walls involved, is known as:

- Cystitis mucosa – catarrh of the bladder
- Interstitial cystitis
- Peri-cystitis; epi-cystitis.

These varieties, however, do not demand detailed and separate descriptions, since they follow one upon the other as grades of intensity of the same morbid process.”

In Germany, Maximilian Nitze (1848-1906), a founding father of modern urology, described the symptoms of a bladder disorder with frequency, pain and inflammatory ulceration of the mucosa, calling it “cystitis parenchymatosa” that caused “heftige Beschwerden” in the patients, published in a textbook in 1907 just after his untimely death at the age of only 57 years.

In 1912, the effect of diet was already attracting attention with the Boston gynaecologist Howard Kelly writing: “Such articles of diet as tomatoes, fruits or acids, should be avoided when the patient finds that they aggravate her condition”.

Meanwhile, the invention of the cystoscope in Europe was revolutionising bladder investigation, paving the way for Guy Hunner and his contemporaries to examine the bladder in greater detail than hitherto possible in living patients - rather than after their demise - without cutting the bladder open.

Guy Leroy Hunner, a Boston gynaecologist, described this “ulcerative”, inflammatory bladder disease in great detail for the first time in a series of papers, the first being published in 1914 (republished in 1915). In this first paper, he writes: *“While cystoscopy usually reveals only one inflammatory spot, there may be two or three granulation areas near together or somewhat separated, and operation usually reveals a more extensive area of inflammation than was appreciated by cystoscopy. The ulcer area may be easily overlooked and the attention may first be arrested by an area of dead white scar tissue. In the neighbourhood of this scar-looking area, one sees one or more areas of hyperemia which, on being touched with a dry cotton pledget, or with the end of the speculum, bleed and first show their character as ulcers. In other cases, or perhaps at subsequent examination on the same case, the ulcer may be well defined as a deeply red area with granulating base and with congested vessels surrounding the area. In none of the cases has an individual ulcer area been more than a half centimetre in diameter, although two or three such ulcers have at times been grouped in a larger inflammatory area.”*

By 1918, not only was cystoscopic technology improving, but Hunner was gaining in experience and had many more patients. In his paper on the “Elusive Ulcer of the Bladder”, he now gives more extensive descriptions of the cystoscopic picture: *“These ulcer areas are always small, usually measuring not more than 5mm. in diameter. They may be linear and measure from 0.5 to 2 cm. in length and from 1 to 2 mm. in width and may thus resemble the mouse-eaten linear ulcer not infrequently found in a tuberculous bladder. Two or three minute ulcers may be found in a group and they may be surrounded by a small red area of edema. The ulcers always appear to be superficial, and I have never seen them covered with necrotic membrane or urinary salts and have never seen them present a picture suggesting malignancy. The ulcer area may or may not be surrounded by a zone of radially converging vessels. One may find a minute ulcer with or without edema around it, and in another portion of the mucosa an edema area without an appreciable ulcer. These edema areas are generally seen immediately after the patient has been having an unusually bad period of bladder symptoms with much strangury.”*

These “ulcers” came to be known as “Hunner's ulcers”, although it was realized very early on that the term “ulcer” was a misnomer since it did not in fact concern a true ulcer but a vulnus and was frequently described by contemporaries as a lesion. Hunner was using either the Nitze or Kelly cystoscope, but vision in those days was relatively poor and this may have been one of the reasons he thought he was seeing ulcers. However, his description of lesions remained the gold standard for many years.

Guy Hunner had deep empathy with his patients, describing their pain as follows: *“The pain is often of the most extreme grade, the patient complaining of a jabbing or stabbing knifelike pain or of a sensation of a jagged, sharp stick in the bladder.” One of his patients “often had such extreme urgency that she had to leave a streetcar in order to enter the nearest house and ask for permission to void.”*

Floyd Keene, gynaecologist of Philadelphia and a contemporary of Hunner, wrote a paper on “Circumscribed Pan-mural Ulcerative Cystitis” published in 1920 in which he described the bladder as having a “flea-bite” appearance in one or more areas.

In 1944 Cristol wrote about 78 cases of interstitial cystitis in men, and in 1950 Heslin also wrote on IC in male patients.

While there were many more publications on this disorder on both sides of the Atlantic in English, French and German in this period, it was John R. Hand who published the first really comprehensive paper on the subject with a report on 223 cases (204 women and 19 men) in 1949. Hand divided the interstitial cystitis patients into 3 grades, based on the severity of the cystoscopic findings: Grade I represents minimal bladder involvement, Grade II represents a more advanced stage of the disease, Grade III represents the most advanced stage of the disease. Hand also described submucosal hemorrhages: *“On distention there were small discrete, submucosal hemorrhages, showing variations in form. Near the trigone, for example, there were dot-like bleeding points”* (the term “glomerulations” was only coined much later in 1978 by Walsh). The symptoms were described as pain, frequency day and night and extreme urgency. At this period, it was still assumed that the milder cases would eventually progress to lesions.

While earlier writers – including Guy Hunner - were aware of possible association with rheumatic diseases, Hand also emphasized that *“allergies were more common among the patients with IC than among those from the general admission.”*

Like all his colleagues, Hand was also concerned with the name of the disease and wrote: *“For some time I have also been impressed with the inadequacy of the many names which have been given to this disease. And after considerable thought, I am inclined to agree with Folsom’s pithy comment that when Hunner “delivered this child into the urologic world he did not name it as well as he described it”.* He continues: *“Without doubt, some phase of the disease gives justification for each of its many names. But no one name yet proposed is wholly satisfactory because it fails to take into account the changing picture of the disease. However, until a better name is found, ‘interstitial cystitis’ is the most suitable...”* Hand can be said to have brought IC into the modern era.

In 1951, the term “painful bladder” first appeared, introduced by J.P. Bourque from Canada as an umbrella term for all disorders causing pain in the bladder including IC.

Two articles on IC in children by Harold McDonald appeared in 1953 and 1958, followed by an article in 1960 on the same topic by Chenoweth.

In 1970, in a paper on new clinical and immunological observations, Oravisto and colleagues wrote: *“Although interstitial cystitis is fairly uncommon, it is not rare and, in our experience, mild and atypical cases readily escape detection”.* Oravisto noted the high frequency of drug hypersensitivity in these patients.

In 1978, a milestone was reached when Chapter 19 of Campbell’s Urology was entirely devoted to interstitial cystitis. Author Anthony Walsh described IC as a *“disease of extremes: extremely severe symptoms; extremes of underdiagnosis; etiologic theories varying from the abstruse to the fashionable; treatment ranging from the alpha of vitamin prescription to the omega of radical bladder substitution surgery; and sadly often, extreme confusion in medical thinking,”* much of which is still valid today.

Walsh felt that the term Hunner’s ulcer should be abandoned because *“it is seriously misleading”* and notes that *“Hunner’s ulcer has led many less experienced physicians to expect to see an ulcer at cystoscopy, and when no ulcer could be found, they erroneously failed to diagnose many genuine cases”.*

Walsh appears to be the first to describe punctuate red dots as “glomerulations” but questions the specificity of glomerulations since *“glomerulation is not absolutely pathognomonic since it has been seen after overdilatation in patients with dyskenesia”.* However, despite Walsh’s possible doubts,

glomerulations continued to be considered a hallmark of IC until the mid-1990s when their diagnostic value came into question once again.

Walsh famously described IC as *“an irritable bladder in an irritable patient”*.

Likewise in 1978, Messing and Stamey reported in great detail on a retrospective review of 52 patients with IC and felt that the majority of patients do not have Hunner’s ulcer. Like Walsh, they also stated that *“we believe that the synonymity of Hunner’s ulcer with interstitial cystitis has done more to prevent recognition of this disease than any other single factor”*.

It is indeed most probably this historic association between Guy Hunner's ulcers and IC that has resulted in many patients with the non-ulcerative type remaining undiagnosed and untreated over so many decades.

In 1987, Fall and colleagues described interstitial cystitis as a “heterogeneous syndrome”. They also reported observing marked clinical differences between ulcerative (classic) and nonulcerative interstitial cystitis: *“These 2 conditions appear to represent separate entities and should be evaluated separately in clinical studies”*

Also in 1987, encouraged by the American Interstitial Cystitis Association (ICA) founded in 1984, the NIDDK in the USA drew up a first consensus definition of IC, revised in 1988. These criteria were specifically intended for research purposes to provide a common basis for much-needed studies and allow comparison between the studies. The criteria were never intended as a definition for the clinician. However, due to the lack of any other guidelines for clinical diagnosis, they were widely used for the diagnosis of patients in a clinical setting. It was later estimated that some 60% of patients with IC symptoms failed to meet these strict criteria, resulting in many patients remaining undiagnosed and consequently untreated. The irony of the situation is that while doctors in the United States mainly stopped using the NIDDK criteria for clinical diagnosis, doctors in other parts of the world continued to adhere to them rigidly due to the lack of any other clear guidelines. An interesting aspect of the NIDDK criteria was that pain was not compulsory: it was either pain or urgency.

Although the name painful bladder (disease) had been around since the early fifties, it was only introduced into standard terminology in 2002 by the International Continence Society (ICS), defining it as *“the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology”*. They reserved the term interstitial cystitis for patients with *“typical cystoscopic and histological features”*. However, the ICS unfortunately did not specify exactly what these typical features were. This led to usage of the combined term IC/PBS or PBS/IC, due to the fact that the ICS definition did not make it any easier to diagnose patients because doctors found it difficult to understand what the distinction was supposed to be between IC and PBS, particularly in countries where it is not customary to perform cystoscopy and/or biopsy in all patients. This definition of PBS was shown by J. Warren to have only 64% sensitivity.

In 2006 the European Society for the Study of IC/PBS (ESSIC) designed a type classification system according to findings at cystoscopy and biopsy and caused some controversy on announcing that it preferred to use the name bladder pain syndrome (BPS) which is a name taken from the urogenital pain taxonomy (classification) of the International Association for the Study of Pain (IASP), a taxonomy which had already been used in EAU Guidelines for chronic pelvic pain.

ESSIC’s definition in 2008 was as follows: BPS would be diagnosed on the basis of chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder

accompanied by at least one other urinary symptom like persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies. The presence of other organ symptoms as well as cognitive, behavioural, emotional and sexual symptoms should be addressed.

In 2008, the NIDDK launched a 5-year multi-centre research programme entitled the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) with an innovative shift in research focus. This research project will study both interstitial cystitis (IC) and chronic prostatitis (CP/CPPS) in a wider systemic framework, exploring in more detail the relationships and overlap with disorders that often co-exist such as fibromyalgia, irritable bowel syndrome, chronic fatigue and vulvodynia and asking whether these associated disorders can provide additional insights into IC/BPS or CP/CPPS. The primary objectives of the MAPP include: to understand the underlying disease pathophysiology and risk factors through targeted epidemiological studies and use of biological samples; and to provide a translational foundation for the development of therapies.

An important part of these studies was to be the *phenotyping* (clinical characterization into types) of patients participating in the studies. The ultimate aim is to arrive at optimum treatment for the individual patient and avoid the current “hit-or-miss” approach. In connection with this study, a new term was recently introduced by the NIDDK: the Urologic Chronic Pelvic Pain Syndromes (UCPPS). For more information on the MAPP study, visit: <http://www.mappnetwork.org/>

The NIDDK MAPP IC Inclusion Criteria are as follows:

- Females or males having an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of at least 3 consecutive months’ duration, in the absence of infection or other identifiable causes.
- Scoring at least 1 on the frequency scale and at least 1 on the pain, pressure, discomfort scale.

The “snowflake hypothesis” appeared in 2009 in relation to both IC and CP, based on the concept that no two patients are the same, just like snowflakes which are all different but still snowflakes. This led to a pilot clinical phenotyping system developed by Nickel, Shoskes and Irvine-Bird known as **UPOINT**. The purpose of this pilot phenotyping system was to classify patients with IC according to clinically relevant domains or subtypes (phenotypes) with the ultimate aim of optimizing therapy and improving outcomes. These UPOINT domains were: **U**rinary, **P**sychosocial, **O**rgan Specific, **I**nfection, **N**eurologic/Systemic, **T**enderness. However, in 2018 this was changed for IC/BPS to **INPUT**: **I**nfection, **N**eurologic/systemic, **P**sychosocial, **U**lcers and **T**enderness of muscles.

The Society of Interstitial Cystitis of Japan (SICJ) and a group of East Asian countries (Japan, Korea, Taiwan) both published detailed guidelines in 2009, in which they both proposed a new symptom complex to be known as Hypersensitive Bladder Syndrome (HBS). This would be a clinical entity that is more inclusive than pain syndromes alone since it incorporates patients with and without pain. The HBS concept was slightly adjusted in 2013. They defined interstitial cystitis (IC) as a disease of the urinary bladder diagnosed by three conditions: 1) lower urinary tract symptoms, such as bladder hypersensitivity, urinary frequency, bladder discomfort and bladder pain; 2) bladder pathology such as Hunner’s ulcer and mucosal bleeding after over-distension; and 3) exclusion of confusable diseases such as infection, malignancy and calculi of the urinary tract. They created the umbrella term of “frequency/urgency syndrome” characterized by frequency (frequent voiding) and urgency (strong desire to void). This is an inclusive term incorporating overactive bladder syndrome, hypersensitive bladder and other conditions associated with frequency and urgency.

In 2011, the American Urological Society (AUA) decided to adopt the name IC/BPS in its guideline “*Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome*”. In the field of diagnosis, it placed the emphasis on exclusion of other diseases or disorders and the symptoms of the patient.

The definition it adopted is as follows: *“An unpleasant sensation, (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes.”* In this AUA guideline, the terms IC and BPS are used synonymously.

This guideline is regularly updated and can be accessed at:

[http://www.auanet.org/guidelines/interstitial-cystitis/bladder-pain-syndrome-\(2011-amended-2014\)](http://www.auanet.org/guidelines/interstitial-cystitis/bladder-pain-syndrome-(2011-amended-2014))

In its 2012 updated Guidelines on Chronic Pelvic Pain, the European Association of Urology (EAU) used the term bladder pain syndrome with the following definition: *“bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy.”* The term IC is reserved for Hunner’s lesion as a specific type of chronic inflammation of the bladder. The latest version of this guideline can be accessed at: <https://uroweb.org/wp-content/uploads/EAU-Guidelines-Chronic-Pelvic-Pain-2016-1.pdf>

At the 1st Sensory Bladder Meeting held at Les Pensières, Fondation Merieux, Veyrier du Lac, France, 22-23 June 2012, J-J Labat from Nantes presented the French hypersensitivity proposal:

- Non-painful visceral hyperactivity syndrome due to visceral hypersensitivity (bladder, bowel)
- Painful pelvic visceral hypersensitivity (bladder, bowel, vulva, urethra, prostate)
- Pelvic non-visceral hypersensitivity (musculoligamentous trigger points, bone (bone tenderness), skin, mucosa (hyperpathia, superficial allodynia))

The book “Bladder Pain Syndrome, A Guide for Clinicians” by the ESSIC group was published in 2013.

The Joint meeting of the 3rd International Consultation on Interstitial Cystitis (ICICJ3) and the ESSIC Annual Meeting 2013, held in Kyoto Japan 21-23 March, 2013, recommended splitting off Hunner’s lesion and calling it by its historic name interstitial cystitis, reserving the term bladder pain syndrome for non/lesion patients. However, the East Asian countries do not like use of the pain term since they believe that patients do not interpret discomfort, pressure and unpleasant sensations as being pain and for this reason they use the term hypersensitive bladder. The meeting emphasised that glomerulations should not be considered diagnostic, they are not specific to IC/BPS and at present no-one knows what causes them or what their significance is. It was also stressed that phenotyping/subtyping is essential for further progress in research and treatment.

In 2015, Wennevik and colleagues concluded that there are no convincing data to show that the presence of glomerulations is specifically related to BPS/IC in Wennevik GE, Meijlink JM, Hanno P, Nordling J. The role of glomerulations in Bladder Pain Syndrome – A review. *J Urol* 2016 Jan 01;195(1)19-25

In 2018, the book Bladder Pain Syndrome – an Evolution. Edited by P.M. Hanno, J. Nordling, D.R. Staskin, A.J. Wein, J.J. Wyndaele was published.

Meetings of ICICJ/SICJ in Kyoto and ESSIC in Florence in 2018 concluded that the lack of international consensus on the name and definition is indeed a problem because consistency in use of terminology is a basic requirement for clear communication in any field of medicine and is absolutely essential for international research. But first we need to understand exactly what disease (or diseases) it is that we are trying to communicate! Further phenotyping or subtyping should help to point the way to better treatment.

In 2019, several papers were published from different parts of the world recommending that Hunner Lesion Disease should be considered a separate entity from non-lesion IC/BPS.

In the meantime, for the sake of continuity and clarity for patients and for others seeking information, the patient organizations are mainly continuing to use the traditional name interstitial cystitis (IC), sometimes in combination with bladder pain syndrome (IC/BPS) or painful bladder syndrome (IC/PBS) and in East Asian countries hypersensitive bladder (HSB).

See also:

Meijlink JM. Interstitial cystitis and the painful bladder: a brief history of nomenclature, definitions and criteria. Int J Urol. 2014 Apr;21 Suppl 1:4-12. doi: 10.1111/iju.12307. Review.

Meijlink JM, Van Kerrebroeck P. Chapter 28: Interstitial Cystitis: from Enigma to International Consensus. In: Milestones in Urology. Eds Felderhof E, Mattelaer JH, Moll F, Schultheiss D, Van Kerrebroeck P. Published by EAU, Davidsfonds Uitgeverij. 2015

CHAPTER 4 - DIAGNOSIS

Referral by family doctor/primary care

Seeking medical help is a series of hurdles and, despite increased awareness, a patient may still spend years without the right diagnosis. The first hurdle is recognition at a primary care level of the possibility that a patient may have interstitial cystitis/bladder pain syndrome. Diagnosing IC/BPS is often a long, complex process that starts with referral to a urologist or urogynaecologist by a family doctor. This means that it is essential to ensure that these family doctors are aware of IC/BPS and its wide spectrum of symptoms so as to ensure referral to the right specialist and hopefully to achieve the right diagnosis and treatment at the earliest possible stage. A primary health provider who may never have heard of IC/BPS will quite likely assume that the symptoms are caused by an infection and repeatedly prescribe antibiotics, even when urine tests for infection are negative. Furthermore, the fact that many patients may have pelvic pain means that in the past many women have been referred to gynaecologists and have consequently been subjected to all kinds of unnecessary treatment including radical gynaecological surgery.

If IC/BPS is suspected, it is advisable for patients and their primary health providers to look for a specialist with expertise and interest in this specific field.

Diagnosis by the urologist/urogynaecologist

At the present time, due to the lack of specific tests or markers, diagnosis of IC/BPS is based on:

- Symptoms: pain or discomfort or pressure or other unpleasant sensation, accompanied by other urological symptoms such as urgency and frequency during the day and night lasting more than 3 months*
- Exclusion of any other identifiable infection, disease or disorder (so-called confusable diseases) that might cause the symptoms. **

** Some definitions say 6 weeks, based on the view that if all other possibilities have been excluded in that time, treatment should be started immediately rather than leaving the patient in pain. Others say a minimum of 6 months.*

*** Nevertheless, it should be taken into account that the diagnosis of a confusable disease does not necessarily exclude a diagnosis of IC/BPS. A confusable disease and IC/BPS may co-exist.*

This diagnosis may be supported by:

- Cystoscopic findings with or without hydrodistension
- Biopsy findings
- Testing to confirm the bladder as the source of the symptoms

Diagnosis of IC/BPS is essentially based on symptoms and exclusion of other painful bladder conditions that resemble IC/BPS but have a different identifiable cause (see confusable diseases).

Two types: Hunner Lesion Disease and non-lesion IC/BPS

However, it may be supported by cystoscopic and biopsy findings, including inflammation, lesions, or general mild oedema which may indicate **Hunner lesion**. If lesions are found, they should be biopsied to rule out any malignancy. Narrow Band Imaging (NBI) is a new way of detecting lesions, currently being applied in Japan.

However, while the bladders of many non-lesion patients with severe symptoms may appear completely normal, this does not mean that there is no - as yet invisible - damage to nerves in the bladder wall, possibly caused by a leaky, defective GAG-layer lining the inside of the bladder.

While glomerulations may be seen in some patients, it should be emphasized that these are not specific to IC/BPS, their significance is still unknown and they therefore cannot be used as a basis for diagnosis on their own, but should nevertheless always be recorded when seen.

Hunner lesion type IC/BPS and non-lesion IC/BPS are currently considered likely to be two separate diseases.

Table 1: ESSIC LIST OF RELEVANT CONFUSABLE DISEASES AND HOW THEY CAN BE EXCLUDED OR DIAGNOSED	
Confusable diseases	Excluded or diagnosed by
Carcinoma and carcinoma in situ	Cystoscopy and biopsy
Infection with: Common intestinal bacteria Chlamydia trachomatis Ureaplasma urealyticum Mycoplasma hominis Mycoplasma genitalium Corynebacterium urealyticum Mycobacterium tuberculosis Candida species Herpes simplex Human Papilloma Virus	Routine bacterial culture Special culture Special culture Special culture Special culture Special culture Dipstick if "sterile", pyuria culture for <i>M. tuberculosis</i> Special culture Physical examination Physical examination
Radiation Chemotherapy, including immunotherapy with cyclophosphamide Anti-inflammatory therapy with tiaprofenic acid	Medical history Medical history Medical history Medical history
Bladder neck obstruction Neurogenic outlet obstruction Bladder stone Lower ureteric stone	Flowmetry and ultrasound Medical history, flowmetry and ultrasound Imaging or cystoscopy Medical history and/or haematuria (→upper urinary tract imaging such as CT or IVP)
Urethral diverticulum Urogenital prolapse	Medical history and physical examination Medical history and physical examination
Endometriosis Vaginal candidiasis Cervical, uterine and ovarian cancer	Medical history and physical examination Medical history and physical examination Physical examination
Incomplete bladder emptying (retention)	Post-void residual urine volume measured by ultrasound scanning
Overactive bladder Prostate cancer Benign prostatic obstruction Chronic bacterial prostatitis Chronic non-bacterial prostatitis	Medical history and urodynamics Physical examination and PSA Flowmetry and pressure-flow studies Medical history, physical examination, culture Medical history, physical examination, culture
Pudendal nerve entrapment Pelvic floor muscle related pain	Medical history, physical examination, nerve block may prove diagnosis Medical history, physical examination
Source: European Society for the Study of IC/BPS (ESSIC) Eur.Urol. 2008 Jan;53(1):60-7. Epub 2007 Sep 20.	

Many of the tests and investigations are aimed at eliminating all other possibilities. For example: urinary tract infections, kidney or bladder stones, bladder cancer, vaginal infections, sexually transmitted infections, radiation cystitis (caused by radiation therapy), chemical cystitis (caused by drugs), eosinophilic cystitis, tuberculosis, schistosomiasis, endometriosis (in women), prostatitis (in men), neurologic disorders including pudendal or other nerve entrapment, and low count bacterial infections that may be missed by dipstick testing.

Ketamine associated cystitis

Street ketamine abuse causing ketamine associated cystitis has also been reported in recent years as a cause of symptoms closely resembling IC/BPS, may cause serious inflammation and lesions and even the need for removal of the bladder (cystectomy). The latter situation is particularly concerning, bearing in mind that these drug abusers are mainly young people. Since use of this cheap drug is spreading rapidly around the world, it is essential for young people to be made aware of the risks to their urinary tract. A fact sheet on Ketamine Abuse and the urinary Tract can be found at: <http://www.painful-bladder.org/pdf/2013-Fact%20Sheet%20ketamine.pdf>

A confusable disease and IC/BPS may co-exist

However, the diagnosis of a confusable disease does not necessarily exclude a diagnosis of IC/BPS. They may exist side by side. IC/BPS patients can of course also get bladder infections, endometriosis etc.

See **Table 1** for a list of relevant confusable diseases as proposed by the International Society for the Study of BPS/IC (ESSIC).

Diagnosis a relief

Many patients will have seen numerous doctors and specialists before finally getting the right diagnosis. Patients who, despite seeing innumerable different doctors, still have no diagnosis can become absolutely desperate with pain, frequency and frustration to the point of being suicidal. Many will have been told time and time again that "it's all in the mind". It can therefore initially come as an immense relief to a patient to be given the diagnosis of IC/BPS, a disease that actually has a name to it. Patients feel that their long history of pain and debilitating symptoms is at last being taken seriously by the medical profession.

WHAT INVESTIGATIONS DOES A UROLOGIST OR UROGYNAECOLOGIST CARRY OUT IN ORDER TO ARRIVE AT A DIAGNOSIS?

This varies from country to country and may be dictated by economic considerations - including the type of healthcare and health insurance system prevailing in a given country - as well as by the medical facilities available. In some parts of the world there is a trend towards basing initial diagnosis on symptoms and exclusions, while other countries routinely perform more extensive investigations such as cystoscopy with/without hydrodistension, and with/without biopsy.

No specific diagnostic tests exist

There are still no diagnostic tests specifically for IC/BPS. However, research in the field of markers looks promising and may eventually produce a diagnostic urine or blood test. Finding a reliable urine or blood marker could substantially speed up diagnosis.

Diagnostic procedures may include

- Medical history including questionnaires
- Physical examination
- Laboratory tests including dipstick urinalysis, routine and special cultures, urine cytology
- Serum PSA in male patients over the age of 40 years
- Flowmetry and post-void residual urine volume measure by ultrasound scanning

- Cystoscopy with biopsy

Medical history: First of all a detailed and careful medical history of the patient is taken with special attention to previous pelvic surgery, any history of urinary tract infections, urological diseases or sexually transmitted infections, any autoimmune diseases, any other chronic pain conditions or other chronic diseases (including e.g. fibromyalgia, irritable bowel syndrome, gastro-esophageal reflux disease, vulvodynia, migraine, facial pain/temporomandibular joint disorder), any previous pelvic radiation treatment, chemotherapy, location of the pain and whether it is related to bladder filling/emptying, description of the pain and whether there is more than one pain generator. Does the patient have any memory of an event that appeared to trigger the first attack, such as a bladder infection, etc?

Does anything specific trigger the flares? Does the patient have pain problems with sexual intercourse (dyspareunia)? Does the patient experience worsening of the symptoms with specific foods or drinks? Is there increased pain with bladder filling. Does the pain increase around menstruation? Does the patient have to urinate during the night?

A history of **previous medication or other drug history** is important since certain drugs have been shown to cause bladder symptoms similar to IC (e.g. tiaprofenic acid, cyclophosphamide and more recently street ketamine abuse (ketamine-associated urinary dysfunction) resulting in ketamine cystitis). This list is not inclusive and does not exclude the possibility that bladder inflammation and/or lesions may have been caused by other drugs prescribed for other conditions.

Patients may be asked to fill in questionnaires about their medical history before their first appointment.

Physical examination: A general physical examination is carried out, including pain mapping. Women will have a vaginal examination and men a digital rectal examination. Evaluation of the pelvic floor is recommended.

Laboratory tests: Urine dipstick and urine cultures will be carried out to check for bacterial infection or infectious diseases including tuberculosis. Special urine, blood or swab tests may be needed to check for the presence of infectious organisms such as Ureaplasma, Chlamydia and Candida which are not detectable with normal urine tests. In men, prostatic fluid may be examined for signs of infection. Urine cytology tests are carried out to check for the presence of malignant cells and to exclude bladder cancer.

Voiding Charts and Questionnaires for symptom evaluation

The patient may then be asked to fill in **voiding charts** with volume intake and output, **symptom and bother scores** or **quality of life scores**. Patients may also be asked to record the pain they have felt in the last 24 hours on a **Visual Analogue Scale (VAS)**. The different questionnaires or scores have the purpose of evaluating the level and nature of the symptoms and their impact on the patient's quality of life. These questionnaires are **not** recommended for diagnostic purposes but are useful for documenting symptoms/quality of life and the patient's progress.

Urodynamics: A urodynamic investigation is sometimes carried out when considered necessary by the urologist but is not considered essential for the diagnosis of IC/BPS. Whether this is done or not varies from country to country. It is, however, considered mandatory in men. This investigation assesses how much urine the bladder can hold and when the patient first feels the desire to urinate and whether this is painful. A thin catheter is inserted via the urethra into the bladder in order to fill the bladder and measure the pressure that builds up in the bladder. A second catheter is placed in the rectum to measure the pressure in the abdomen. This investigation is also carried out if the

patient is suffering from any kind of urinary retention or obstruction and either unable to empty the bladder at all or only able to partially empty it.

Imaging: Ultrasound scanning may be carried out to see how much urine is left in the bladder after urination (post-void residual urine).

Cystoscopy: This procedure allows the urologist to look inside the bladder and carry out a number of tests and is a standard investigation in urology. A narrow tube is inserted into the bladder via the urethra. It has two or more channels: one carrying an endoscope that allows visual examination of the inside of the bladder, the other channel carries fluid for instillation into the bladder. Narrow Band Imaging currently being used in East Asia/Japan is believed to be more effective in detecting lesions.

There are two main methods of cystoscopy:

- office cystoscopy using local anaesthesia but without hydrodistension* and
- cystoscopy under general or spinal anaesthesia with hydrodistension.

* hydrodistension = stretching the bladder by slowly filling with water.

While cystoscopy is recommended as a standard investigation for IC/BPS in many parts of the world, in some countries including the USA even office cystoscopy is often only carried out if the patient has blood in the urine (haematuria) and it is therefore necessary to rule out the possibility of cancer or other disorders, or if the patient has failed to respond to conservative measures or first line treatment.

- **The office cystoscopy with local anaesthesia** is an investigation to exclude the possibility of other causes of the symptoms, such as tumours, stones, eosinophilic cystitis etc. Office cystoscopy also makes it possible to detect any scarring or cracking of the bladder wall or red patches which might be **Hunner lesion**. This is particularly important since Hunner lesion responds well to specific forms of treatment. At the same time the urologist will take a look at the urethra. In women a gynaecologic examination may be carried out and in men palpation of the prostate.
- **Cystoscopy under general or spinal anaesthesia**, commonly done in Europe and East Asia, is performed when IC/BPS is suspected in order to carry out **hydrodistension** in which the bladder is filled with fluid twice, the first time to maximum capacity to assess bladder capacity under anaesthesia, the second time filled less in **order to inspect the bladder wall**. Hydrodistension's main role lies in the diagnosis of Hunner lesion. Hydrodistension may produce glomerulations in the bladder wall in some patients, but glomerulations are not specific for IC/BPS and cannot be considered diagnostic, see further below. In some countries, it is currently questioned whether hydrodistension is relevant as a routine clinical investigation, while in other countries it is compulsory. Hydrodistension is sometimes used successfully in selected patients as a form of treatment and can provide temporary relief.

Findings from cystoscopic investigations may include:

HUNNER LESION DISEASE

- **Hunner lesion (formerly known as Hunner's ulcer, Ulcerated IC and sometimes referred to as Classic IC, Hunner Lesion Disease, Hunner IC)**

Hunner lesion is a specific type and currently considered likely to be a separate disease. The historic term "ulcer" is misleading and confusing since it is not usually a true ulcer, but an inflammatory lesion, also known sometimes as a "patch". Bladder distension will cause any scar-like lesions to crack and bleed. While this Classic type of IC with lesions is believed to be less common than the

non-lesion type, if present it will best be fully identifiable during cystoscopy with hydrodistension although some experts believe that many lesions can be successfully seen without hydrodistension.

It is possible that these lesions are being under-diagnosed. Every effort is currently being made to ensure that urologists and urogynaecologists can identify Hunner lesions in the bladder when they see them. Narrow Band Imaging may improve the rate of diagnosis.

Professor Magnus Fall from Sweden has described these lesions as follows on the ESSIC website:

“The Hunner lesion typically presents as a circumscribed, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area. This site ruptures with increasing bladder distension, with petechial oozing of blood from the lesion and the mucosal margins in a waterfall manner. A rather typical, slightly bullous edema develops post-distension with varying peripheral extension.”

A further detailed description can be found on in the book: *Bladder Pain Syndrome, A Guide for Clinicians*. Edited by J. Nordling, J.J. Wyndaele, J.P. van de Merwe, P. Bouchelouche, M. Cervigni, M. Fall. Published 2013.

It is particularly important for these bladder lesions to be identified as soon as possible in patients with IC/BPS symptoms as **Hunner Lesion Disease** responds well to specific treatments.

Glomerulations are no longer considered diagnostic

Glomerulations are pinpoint petechial haemorrhages, only seen after distension of the bladder. While glomerulations – first named as such by Walsh in *Campbell's Urology* in 1978 - were once thought to be typical of IC/BPS, they have since then also been found in patients with normal bladders, in patients who have had for example radiation therapy, bladder cancer, exposure to chemotherapy or toxic drugs, while some patients with all the symptoms of IC/BPS have no sign of glomerulations in their bladder at all. Glomerulations are therefore no longer considered diagnostic of IC/BPS. However, when they are found, they should always be recorded.

See: *Wennevik GE, Meijlink JM, Hanno P, Nordling J. The role of glomerulations in Bladder Pain Syndrome – A review. J Urol 2016 Jan 01;195(1)19-25.*

Other investigations:

Biopsy:

A bladder biopsy may be carried out. If hydrodistension is performed, biopsy should be done following the hydrodistension and never before due to the risk of perforation. Biopsy involves taking a minimum of three small samples of tissue from different levels in the bladder wall, including from the detrusor muscle, at several different sites in the bladder. These samples will then be examined microscopically by the pathologist and may reveal an increase in mast cells in the detrusor muscle in the bladder wall. Mast cells play a role in allergic and inflammatory reactions in the body's tissues. They can degranulate and release histamine. Mast cell counts may often be higher in IC/BPS patients than in patients with other bladder diseases but are not considered to be sufficiently specific to be used as a diagnosis alone.

However, completely normal biopsy results may be found in some patients who do not have Hunner lesions.

The biopsy is important to exclude the possibility of other causes of the symptoms (such as bladder cancer, eosinophilic cystitis and tuberculous cystitis) and all lesions or patches should therefore be biopsied. Biopsy is more likely to be routinely carried out in Europe and Japan than in the USA for example. While cost may play a role here, it is also considered an invasive procedure by some and will then only be performed if the symptoms fail to respond to first line conservative treatment.

Potassium sensitivity test:

The potassium sensitivity test which was studied for some time as a potential way of diagnosing IC/BPS is **no longer recommended** for diagnostic purposes as it is too painful for the patient. A milder, **modified** form of this potassium test was developed as a possible way of selecting patients who may respond well to intravesical treatment aimed at temporarily replenishing the lining of the bladder (so-called GAG-layer).

The above tests can temporarily exacerbate the symptoms and cause burning in the bladder, urethra and when urinating for several days or longer, with blood visible in the urine. A bladder biopsy may cause a burning sensation for several weeks until the lining of the bladder has fully recovered.

Anaesthetic challenge test:

Instillation of (alkalized) lidocaine into the bladder – also used as a rescue therapy with or without heparin to calm extreme pain in the bladder - is increasingly being used to assess whether the pain is actually in the bladder or elsewhere. If the pain is coming from the bladder, it will be anaesthetized by the lidocaine.

Reassessment

If a patient fails to respond to treatment for IC/BPS, reassessment is recommended to see if any lesions or any other disease or disorder have been missed.

Important: Negative test results do not necessarily mean that a patient does not have IC/BPS

Even after all these investigations have been carried out and if the results are negative, this still does not necessarily mean that the patient does not have IC/BPS. Some patients may exhibit no abnormalities during the above investigations, while nevertheless displaying all the characteristic symptoms of interstitial cystitis. The most important part of the investigations is to exclude all other identifiable causes of the symptoms (so-called confusable diseases).

Exclusion of confusable disorders + IC/BPS symptoms = IC/BPS.

Note: Cystoscopic findings often bear no correlation to the patient's symptoms. There may be very severe symptoms with little or nothing to be seen cystoscopically. This does not mean, however, that there is no nerve damage for example inside the bladder wall.

CHAPTER 5 – TREATMENT

Once a diagnosis of IC/BPS has been established, the doctor then has the task of explaining to the patient that treatment is aimed at alleviation of symptoms and improving the patient's quality of life. Despite all the research and studies that have been carried out, no possibility has yet been found of curing this disease, nor is there a single drug that is effective in all patients. Nevertheless, there are many different options to try. Personalized treatment tailored to the individual is the keyword. Some IC/BPS patients have multiple disorders and may be receiving treatment from several different doctors. It is therefore essential for treatment to be multidisciplinary and coordinated to ensure that the patient is not receiving a potentially harmful combination of drugs. When treating IC/BPS, it is also important for the existence of associated disorders (comorbidities) to be taken into account as these may influence the treatment pathway.

Treatment may consist of: patient education and patient empowerment, diet modification, behavioural changes and stress reduction, bladder retraining, one or more oral drugs, topical drug treatment, bladder instillations or intramural injections, bladder distension, neuromodulation/electrotherapy, surgery, different forms of physical therapy and mind-body therapy, myofascial therapy, trigger point therapy and pelvic floor relaxation, acupuncture, guided imagery, exercise, sex therapy and/or relationship counselling to help sexual problems.

Treatment of IC/BPS should focus on:
a) the pain and
b) urological symptoms such as urgency and frequency.

Treatment specifically for **Hunner lesion** includes laser therapy, fulguration/electrocoagulation, transurethral resection or submucosal injection (of triamcinolone).

Pain management should play an important role. If the pain is very severe and fails to respond to standard treatment, a pain clinic referral may be advisable. No patient should be left in pain!

Treatment is highly individual because every patient is different. A drug that has a beneficial effect on the symptoms of one patient sometimes has no effect on another patient. This is yet another reason for suspecting that IC/BPS may be a multi-factorial disease or a collection of sub-types with similar symptoms. The different treatments may be based on theories concerning the cause, the results of scientific studies or trials, practical experience with specific medications or sometimes purely to treat individual symptoms. The hope for the future is that current research into phenotyping/subtyping will ultimately produce phenotypes or subtypes that will aid more effective treatment per type. At present, patients are basically divided into those with Hunner lesions and those without Hunner lesions.

Medicine intolerance to varying degrees - including extreme forms of multiple drug and chemical intolerance - can be a problem in some patients and make treatment – particularly oral treatment – very difficult. This is very frustrating for both the doctor and patient. While a few patients may have a true allergy, in most it is an intolerance or non-allergic hypersensitivity that may include confusion, dizziness, faintness, balance problems, hyperventilation, nausea, intestinal upsets, blurred eyesight, extreme fatigue or drowsiness/sedation even at very low dosages. All treatment is consequently going to be a question of trial and error since allergy tests are not likely to produce any useful results. For oral drugs, it is best to start at the lowest possible dosage, with just a fraction of a tablet. This naturally does not apply to any necessary antibiotics which always have to be taken as prescribed. However, intravesical treatment may be the best option for some of these patients. It is perhaps interesting to note that this multiple drug intolerance is also found in some patients with fibromyalgia.

Many treatments tried

Over the years, a large number of treatments have been tried for IC/BPS patients, but only a few have reached a higher level of recommendation, and even those are only effective in some patients. This was an important reason for the current Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network study being carried out by the NIH/NIDDK in the USA, aimed at phenotyping or subtyping patients with the aim of finding optimum treatment for each subtype. See: <http://www.mappnetwork.org>.

Symptom-driven treatment

Different patients may experience more bother from different symptoms: for example, one patient may find the persistent and/or urgent need to urinate to be the worst aspect, another finds the lack of sleep and consequent exhaustion due to getting in and out of bed all night to go to the bathroom totally intolerable, while a third may experience the pain as the worst aspect. Since every patient is different, treatment needs to be tailored to each patient. Treatment is symptom-driven and in order to maximize the effects of treatment, it is important to determine which symptom or symptoms are causing the most bother at each stage of the disorder in each individual patient.

Evaluation of treatment is hampered by the spontaneous flares and remission of symptoms that are so characteristic of IC/BPS. It is therefore sometimes very difficult to assess whether an improvement has been caused by the treatment or simply by a spontaneous remission.

Patient education

Patient education plays an important role in any chronic disorder. By learning more about their condition through patient information, websites and support groups, patients can gain a better understanding of their symptoms and are reassured that they are not the only person in the world with this bladder disorder. This can be a first step along the path of acceptance, of learning how to cope and towards empowerment of the patient. Informed patients are also likely to understand much better why they are receiving a specific treatment and what this treatment is aiming to achieve.

Diet modification

Many patients will soon discover from their own experience that certain foods and beverages appear to exacerbate their bladder symptoms. Every patient is different and not all IC/BPS patients appear to be affected by diet, but by eliminating items known to cause irritation based on their own experience, a patient can at least avoid unnecessary exacerbation of the bladder symptoms. Patients with milder IC/BPS may even find that diet modification is the only treatment they need. They can try an elimination diet, starting with a very bland diet and gradually adding food items one at a time.

Table 2: DIET MODIFICATION - The effect of food items on the bladder is highly individual but foods best avoided by IC/BPS patients include:

Food/drink containing caffeine
Citrus fruit and juices
Other acidic food such as tomatoes, vinegar etc.
Artificial sweeteners
Alcoholic drinks
Carbonated drinks/soda
Highly spiced food especially containing hot pepper

Source: *Effects of Comestibles on Symptoms of Interstitial Cystitis*, Barbara Shorter, Martin Lesser, Robert M. Moldwin, Leslie Kushner. *Journal of Urology*, July 2007, vol. 178, 145-152.

There are, however, some guidelines regarding what foods and beverages are most likely to exacerbate symptoms. A study on the effects of food and drink was published in July 2007: **Effects of Comestibles on Symptoms of Interstitial Cystitis**, Barbara Shorter, Martin Lesser, Robert M. Moldwin, Leslie Kushner. *Journal of Urology*, July 2007, vol. 178, 145-152. This study was based on a questionnaire distributed to a group of patients. The aim was to see whether certain foods, beverages and/or dietary supplements affected symptoms of IC/BPS either positively or negatively. 154 foods/drinks were studied. It was concluded that there does indeed appear to be a large number of IC/BPS patients whose hypersensitive bladder symptoms are exacerbated by consumption of specific foods and beverages.

The study identified the most bothersome foods as being items containing **caffeine, citrus fruits and juices, tomatoes and tomato products, items containing vinegar and alcoholic beverages**. Coffee was found to be the most bothersome. The study indicated that exacerbation appears to be worse in foods that contain hot pepper (for example Indian, Mexican and Thai food) suggesting that some component of hot peppers may be causing the exacerbation of symptoms. Patients participating in the study varied greatly regarding the effects of fruits and juices. Some patients are known to experience relief through taking alkalizing agents such as calcium glycerophosphate (Prelief) if available or baking soda (bicarbonate of soda): 1 teaspoon in a glass of water, but since baking soda has a high salt content this should not be taken by patients with salt restrictions.

Table 2 summarises the main foods and beverages that may exacerbate the bladder. But these are simply guidelines and the patient needs to find out what seems to exacerbate his/her own personal bladder symptoms.

A second article reviewing of diet in IC/BPS patients was published in 2012: **Diet and its role in interstitial cystitis/bladder pain syndrome (IC/BPS) and comorbid conditions**. Friedlander JI, Shorter B, Moldwin RM. *BJU Int.* 2012 Jun;109(11):1584-91. The authors suggest that “a controlled method to determine dietary sensitivities, such as an elimination diet, may play an important role in patient management.” They also suggest that co-morbid conditions should be taken into account since these may influence diet sensitivities.

- Not only food and beverages...

Some patients also find that their bladder symptoms increase when taking certain **oral drugs**, for example antibiotics (and certain food supplements such as Vitamin C tablets). If it is a short-term drug, it is a question of gritting your teeth for a week or so. But any drug that exacerbates bladder symptoms and needs to be taken daily over a longer period can better be changed for something else.

- Fluid intake

Before going out anywhere, IC/BPS patients are quite likely to restrict their intake of liquid beforehand. If they have to be away for a few days, they may tend to cut down their fluid intake so much that they become dehydrated, their urine consequently becomes concentrated and this may cause even more pain. Always at the back of their mind is the fear of not being able to find a toilet in time and consequently developing so much pain or discomfort that they can't cope with the situation. Since no patient wants to put him/herself in that position, they develop coping strategies for different situations and this includes not drinking. It is nevertheless important to maintain a balanced fluid intake. While restricting drinking in the evening can help to reduce the need for night-time urination, it may lead to concentration of the urine and more pain!

- Keeping bowels healthy

Avoid constipation at all costs is the motto! Since constipation can exacerbate symptoms by causing pressure in the pelvic floor area, it is essential for IC/BPS patients to try to ensure that their diet

contains sufficient fibre in addition to drinking enough fluids and to take sufficient **exercise** in some form. Many IC/BPS patients also suffer from irritable bowel syndrome (IBS) which may take the form of constipation or diarrhoea or both intermittently, sometimes with painful abdominal cramp. In this situation, a high fibre diet may actually cause more pain and bloating. If a high fibre diet is impossible because it causes bloating and spasms, mild laxatives may be necessary. Some of the drugs used to treat IC/BPS may have constipation as a side effect (including many painkillers/opioids and tricyclic antidepressants).

Lifestyle

- Behavioural changes, stress reduction and relaxation therapy

Patients soon learn that in addition to diet the symptoms of IC/BPS can also be exacerbated by physical or emotional stress which can trigger a flare-up. They consequently need to learn to pace themselves and try to avoid situations which make them physically or emotionally exhausted, while at the same time getting sufficient physical exercise. Adequate treatment for the most bothersome symptoms can also help stress reduction, since not only chronic pain, but also urgency and frequency are very stressful and physically exhausting.

Some patients may find professional counselling of value to learn how to cope with the impact of the disease on their lives and reduce the stress, depression and anxiety which the disease causes. Relaxation techniques, yoga and meditation may all help.

- Clothing & hygiene

IC/BPS patients often feel more comfortable in loose clothing and particularly in cotton underwear, not synthetic underclothes. They have to be careful about the type of washing agent they use for their underwear since washing products and fabric softeners containing perfume can cause irritation. The same applies to their body: no perfumed products near the urogenital area. Patients suffering from vulvodinia, vulvovaginal/perineal pain or sexual pain should be particularly careful about potential irritants such as soaps, powders, shampoo, hair conditioners, shower gel, intimate sprays, detergents and fabric softeners, deodorant tampons and even adhesive on the back of minipads.

- Adapting lifestyle

IC/BPS frequently means a change in lifestyle. A patient has to learn to adapt to the needs and the situation created by the bladder problem. With mild IC/BPS, these changes may be minimal; with severe IC/BPS, the disease may have an impact on all aspects of life. It is nevertheless important for the patient to try to maintain as normal a lifestyle as possible and to develop new interests to replace activities they feel they are no longer able to undertake due to their bladder disorder.

- Relationships and intimacy

Sex therapy and/or relationship counselling may help some patients to deal with intimacy problems.

- IC/BPS in the elderly

IC/BPS may cause additional problems in the elderly. Frequent urination at night may be hazardous and lead to the risk of falls and fractures. A commode chair placed next to the bed could be an option here. Some of the medications used to treat IC/BPS and overactive bladder can have cognitive side-effects which may be more pronounced in the elderly and further exacerbate any existing memory impairment or confusion.

ORAL TREATMENTS

Various oral treatments (tablets, capsules or syrup) are used for IC/BPS. The advantage of oral treatment is that it is easy to administer and non-invasive. However, there are also a number of

disadvantages. When medication is given orally, it is absorbed by the body. The desired effect may be achieved via the blood or via the urine when the active medication has been excreted through the kidneys. This naturally takes some time and relatively little of the medication may actually reach the bladder or stay there for long enough to be effective. The fact that the drug is absorbed into the bloodstream means that side-effects may also occur in other organs. All drugs (including herbal or natural remedies) can potentially have side effects and, as already mentioned, some IC/BPS patients have a problem with multiple drug intolerance.

While some doctors prefer the so-called multimodal approach, aimed at alleviating the different symptoms of pain, frequency and urgency with a cocktail of different oral drugs, others prefer to try one drug at a time, often starting with low doses and slowly increasing to the maximum toleration level. The single drug approach will be better in patients with drug intolerance problems.

Oral treatment may consist of one or more of the following (alphabetical order):

- antidepressants
- anti-inflammatory drugs (including corticosteroids)
- antispasmodics and anticholinergics
- anticonvulsants
- histamine-receptor antagonists
- immunosuppressive agents
- painkillers (analgesics)
- pentosan polysulfate sodium
- prostaglandins

The drugs are discussed below in alphabetical order.

Antidepressants (tricyclic)

This mainly concerns **amitriptyline**, but nortriptyline and doxepin are also used. Tricyclic antidepressants, now widely used in the treatment of chronic and neuropathic pain, are used in the treatment of IC/BPS because they are believed to block the release of histamine, block reuptake of serotonin + norepinephrine, are sodium channel blockers, have central and peripheral anticholinergic action and alleviate pain. They may also have a relaxing effect on the bladder, thereby reducing the desire to urinate and consequently frequency. Patients who have a reasonable bladder capacity appear to respond better to this medication.

- **Amitriptyline** is currently recommended as a standard first-line oral treatment for the pain of IC/BPS, is generic, inexpensive and widely available. It should be taken at dinner in the evening and will help the patient to sleep. By taking at dinner time rather than just before going to sleep, morning hangover can be avoided. This drug is believed to have multiple qualities including pain relief, anticholinergic effects and neuromodulation. It is usual to start with a low dosage (10 mg or less) and gradually increase to optimum toleration level (with minimum side effects) for the individual patient (up to maximum 75 mg). Side effects can be a major drawback and include constipation, dry mouth, urinary retention, weight gain, palpitations and daytime drowsiness.

Anti-inflammatory drugs

While there appears to be a subtype of IC/BPS patients without inflammation who will not respond to anti-inflammatory drugs, bladder inflammation has always been held to be a typical feature of IC/BPS. There are several different groups of anti-inflammatory drugs including the following.

- **Corticosteroids** (e.g. hydrocortisone, prednisolone and dexamethasone) are a group of drugs with a strong anti-inflammatory effect. Although prolonged use can lead to the risk of serious side-effects such as osteoporosis and lowered resistance to infection, these drugs can nevertheless be of great benefit to some patients. While a study indicated that prednisolone may be very effective in pain control in refractory patients with bladder lesions, it may also show (even radical) benefits in IC/BPS patients with a history of associated autoimmune disease.
- **Montelukast** (e.g. Singulair®), a medication used to treat asthma, inhibits the release of leukotrienes from mast cells and other cell types and thereby prevents inflammation. Danish studies showed that treatment of IC/BPS patients with a daily dose of montelukast showed a significant improvement in urinary frequency and pain. There has recently been a revival of interest in montelukast. However, more clinical trials with a larger number of patients are needed for its mechanism to be better understood in IC/BPS.
- **NSAIDs** inhibit the production of prostaglandins, substances that play an important role in stimulating inflammation and in physiological processes in blood platelets, gastric mucosa and kidneys. In addition to their anti-inflammatory effect, NSAIDs also relieve pain but may also cause undesirable effects such as gastrointestinal ulcers and bleeding, fluid retention and hypertension. Examples are aspirin, diclofenac, naproxen and ibuprofen. New NSAIDs, the so-called coxibs, have fewer gastrointestinal side-effects than the old drugs. NSAIDs should not be taken on an empty stomach and pre-treatment to protect the stomach (for example proton pump inhibitors) may be necessary. Most old and the new NSAIDs increase the risk of ischaemic vascular disease.
 - There have been reports, backed up by studies, that the NSAID **tiaprofenic acid** may cause symptoms in some people similar to those of IC/BPS.
- **Quercetin**: this bioflavonoid is an alternative strategy for the treatment of IC/BPS. It is believed to have anti-inflammatory effects and to inhibit the activation of mast-cells. Has shown promising results and is available over the counter (OTC).

Investigational:

- **IP 751** (ajulemic acid): an experimental anti-inflammatory, marijuana-derived analgesic drug currently being developed for various specific conditions including IC/BPS. IP 751 is a non-psychoactive synthetic cannabinoid that appears to suppress inflammation and pain. Unlike many NSAIDs, IP 751 does not appear to cause gastrointestinal ulceration.
- **MN-001**: this is an oral anti-inflammatory compound being developed in the USA for the treatment of IC and bronchial asthma.
- **Tanezumab**, a humanized monoclonal anti-nerve growth factor antibody, is a single-dose intravenous drug that recently underwent clinical trials to reduce pain in IC/BPS patients. However, while the trial was terminated in November 2010 due to potential safety issues, it is still on the agenda.

Antispasmodics and anticholinergics

Antispasmodics and anticholinergics are used to relax the bladder muscle. Commonly used drugs in this category include: darifenacin, solifenacin, tolterodine, trospium, oxybutynin (also available in a transdermal patch form), propiverine and the newer fesoterodine fumarate. These are standard drugs for treatment of overactive bladder syndrome (OAB) but may be effective in some IC/BPS

patients as part of combination treatment, and particularly in patients with overlapping IC/BPS and OAB.

- **Oxybutynin** is an older anticholinergic drug, but now available in a transdermal patch system and extended release tablets. A problem recently discovered with patches is the occurrence of erythema and pruritus at the site where the patch is placed. Side effects have always been a problem with this drug.
- **Tolterodine**, also an anticholinergic drug, was developed for the treatment of overactive bladder. Tolterodine is claimed to have fewer adverse effects (e.g. dry mouth) than oxybutynin and may be of use in some early stage IC/BPS patients.
- **Trospium chloride**, a drug used for overactive bladder symptoms, may also be useful in IC/BPS patients with an urgency-frequency problem. Trospium works by blocking cholinergic receptors found on muscle cells in the bladder, thereby preventing the action of acetylcholine. This relaxes the bladder muscle and helps make the bladder more stable. Newer drugs in this category such as darifenacin and solifenacin are said to have fewer side-effects and are better tolerated.

Although these drugs may have a sedative effect on the bladder in some patients, longer-term use has been found to lead to bladder retention/difficulty in urination by patients. All the drugs in this group tend to have bothersome side effects, the most common of which are dry mouth, dry eyes, dry nose, blurred vision, headache, constipation, drowsiness, dizziness and palpitations. Cognitive side-effects can also occur and are particularly a problem in the elderly. Drug therapy maximum dose is usually determined by the patient's tolerance of side effects. The newer drugs and once-daily drugs have fewer side effects.

Anticonvulsants:

- **Gabapentin** (Neurontin®) is an anticonvulsant medication used to help control certain types of epileptic seizures that has been found to be useful in the treatment of neuropathic pain and postherpetic neuralgia. Experimentally used for IC/BPS and other genitourinary pain, it may have good results in some IC/BPS patients with severe pain and reduce dependence on opioids. A newer drug on the scene in this category is **pregabalin** (Lyrica®) which is also being used for some IC/BPS patients. A common side effect of these drugs is drowsiness/sedation.

Immunosuppressive agents:

- **Cyclosporine A** belongs to the group of medicines known as immunosuppressive agents that suppress the immune system and reduce the immune system's ability to produce certain reactions that can cause inflammation and tissue damage. This drug is normally used to prevent rejection of organ transplants and as a treatment for severe psoriasis, rheumatoid arthritis and many other autoimmune diseases. Recent small studies with low dose cyclosporine A have shown that it may be effective in some IC/BPS patients but should only be used in the most severe cases that have failed to respond to other therapy since side effects can be severe.
- **Tacrolimus** is currently being used in studies and may be promising in some patients. See intravesical treatment.

Histamine-receptor antagonists

There are two types of receptor for histamine, known as H1 and H2. Drugs that block the H1-receptor are also known as **antihistamines**.

- **Hydroxyzine:** The use of the H1-receptor antagonist hydroxyzine is based on the hypothesis that the histamine released by the mast cells is responsible for the symptoms of IC/BPS. Increased levels of mast cells have been found in the lining of the bladder of some IC/BPS patients, possibly a sign of an allergic or autoimmune reaction. Hydroxyzine inhibits mast cell release of histamine and has sedative properties. This type of treatment may be useful in patients with a history of allergies. It requires up to 3 months for an effect to be seen. Dosage: 10 to 25 mg every night at bedtime for a week; then up to 75 mg a day. Can cause drowsiness and in the elderly confusion.
- **Cimetidine and ranitidine** are H2-receptor antagonists or blockers that were mainly used in the treatment of peptic ulcers and acid indigestion. However, while they appear to be useful in alleviating the pain and symptoms of some IC/BPS patients this has never been definitively proven. They are nevertheless recommended in many guidelines.

L-Arginine occurs naturally in the body as an amino acid, one of the building blocks of protein, and plays a role in supplying the body with nitric oxide used by the body to keep blood vessels dilated and improve the blood supply. Its use is controversial and studies suggested that it may have little effect in IC/BPS. However, it has recently re-emerged in research studies, so should not be written off.

Painkillers (analgesics)

Pain management is a very important aspect of treatment of IC/BPS patients. However, some may cause sedation and drowsiness.

- **Standard over-the-counter (non-prescription) painkillers** may help if the pain is mild.
- **Cannabinoids** (drugs based on cannabis) where permitted and available. Also used in oromucosal spray form or vapour. Treatment with cannabis-based medicines may be associated with central nervous and psychiatric side effects.
- **Methotrexate** has shown a significant improvement in pain in IC/BPS patients but had no effect on urgency or frequency.
- **NSAIDs** follow non-prescription painkillers as the next level of pain treatment (see under NSAIDs).
- **Opioids:** In cases of extreme pain that fails to respond to other treatment, long-acting opioids may be necessary (tramadol, morphine, oxycodone, oxymorphone, hydromorphone, fentanyl). Opioids are potent analgesics and are used to relieve the most severe pain. A problem with opioids is that they can cause side effects including fatigue, constipation, nausea as well as dependency. When considering treatment with opioids, potential benefits should be weighed against the risks. Chronic opioid therapy should be considered as a last resort and can best be undertaken in a pain management clinic. Continual evaluation and monitoring is required. Patients should be counselled about the risk of driving and undertaking certain work when being treated with opioids.
- **Painkillers in the form of suppositories** can also be used (paracetamol, paracetamol with codeine) and are sometimes advisable for patients with gastric disorders. **Patches** on the skin are another method. A patient-activated pain device to administer medication for hard-to-treat chronic pain is also available in some countries.
- **Palmitoylethanolamide (Normast®)** is a relatively new painkiller with anti-inflammatory and anti-pain effects for chronic pain conditions and is claimed to have negligible side effects. Available in tablet form or as powder in sachets.
- **Phenazopyridine** is a urinary tract analgesic used for short-term relief of pain in the bladder. Not advisable for long-term treatment as it can build up in the body and cause harmful side effects.

- **Tapentadol** is a new opioid analgesic available as a standard-release tablet for moderate to severe acute pain and as a prolonged-release tablet for severe chronic pain. It is said to have fewer side effects than comparable opioid-based drugs.

*Studies have shown that recreational abuse of the anaesthetic/painkiller **ketamine** (“street ketamine”) can cause pelvic/bladder pain, a small erythematous bladder with ulcerative cystitis, urgency and frequency. This is known as ketamine-associated urinary dysfunction or ketamine cystitis. Clinical use of ketamine (in much lower doses than street ketamine) is not believed to have any detrimental effect on the bladder but should nevertheless be used with caution.*

Referral to a pain management clinic should be considered for the treatment of severe chronic pain particularly if chronic opioid therapy is required.

Pentosan polysulfate sodium (PPS)

PPS is a heparinoid drug. One of the hypotheses concerning the causes of IC/BPS is the existence of a defect in the glycosaminoglycan (GAG) layer that acts as a protective lining for the wall of the bladder. It is believed that PPS temporarily repairs this defect, creating a synthetic layer that protects the underlying bladder wall from being attacked by irritant elements in the urine. Studies suggest that it may also have an anti-inflammatory effect. This medication is obtainable in tablet or capsule form in the United States and Europe under the name Elmiron®, in Italy as Fibrase®, in Germany as SP54® and South Africa and other African countries as Tavan 54®, in India as Comfora and Cystopen, in Korea as Jelmiron. It is also available in many countries for veterinary purposes.

PPS is often used in combination with amitriptyline and hydroxyzine as “multimodal” therapy. A number of studies have been carried out in with the oral form and while they have produced contradictory results appear to have a beneficial effect in some patients. PPS takes some time to show an effect, usually only after 12-16 weeks of treatment. Studies have indicated as long as 6 months. The duration of treatment is now considered to be of more importance in relation to efficacy than any increase in the daily dose. It is used as a second-line treatment, when other oral drugs have failed to show any improvement. This drug is difficult to obtain in some countries. See also intravesical treatment. Possible side effects include reversible hair loss, gastrointestinal pain, diarrhoea and nausea, rash, and dizziness. Recent studies indicated that long-term use may cause eye problems (retinol maculopathy) in some patients. A regular eye-check with an ophthalmologist is therefore recommended, particularly if any eye problems are being experienced. Dosage: 100 mg three times a day.

Prostaglandins:

- **Misoprostol**, an oral prostaglandin E₁ analogue, used to treat gastric ulcers resulting from the use of certain NSAIDs, has also been found successful in treating some IC/BPS patients.

Suplatast tosilate (IPD-1151T)

An anti-allergic agent from Japan, efficacious for allergic diseases, that inhibits the release of histamine and tumour necrosis factor alpha. While early reports from Japan suggested it increased bladder capacity and improved symptoms, without serious side effects, a later study showed no significant difference between this treatment and placebo. However, this applies to many treatments for IC /BPS. It is still in use and may be of value in allergy-prone patients.

TOPICAL TREATMENT (ON THE SKIN)

- **Amitriptyline**, commonly used as an oral drug to treat pain in IC/BPS patients, is also available as an analgesic gel to apply topically on the skin

- **Oxybutynin** is now available in a gel form (Gelnique®) and is applied once daily to the thigh, abdomen, upper arm or shoulder once a day. Side effects include dry mouth and local irritation. While generally used for OAB patients, some IC/BPS patients with predominantly urgency/frequency problems may benefit.
- **Transdermal (skin) patches:** A number of drugs, including lidocaine and oxybutynin, are available for the treatment of pain or urgency/frequency in the form of adhesive skin patches. There can be local side effects such as redness and itching.

VAGINAL & RECTAL TREATMENT FOR PAIN

- **Valium:** Some doctors are prescribing vaginal valium suppositories or tablets to help relieve the pain of pelvic floor dysfunction, interstitial cystitis/bladder pain syndrome, vulvar pain and sexual pain. This causes less drowsiness as a side effect than oral valium, but nevertheless may still produce mild sedation. Dosage is usually 5-10 mg valium compounded (in a paraffin base), starting once nightly and titrating. This treatment can also be used rectally.
- **Rectal** suppositories for pain also include paracetamol, diclofenac and opioids.

SUBCUTANEOUS INJECTION: Experimental Treatments

- **Adalimumab** is an anti-inflammatory agent being studied for IC/BPS. This is an injectable medication given subcutaneously. It is a tumor necrosis factor (TNF) blocker, approved since the end of 2002 for the treatment of rheumatoid arthritis, psoriasis, ankylosing spondylitis, and Crohn's disease.
- **Omalizumab** is used for severe allergic conditions and is currently being investigated for use in IC/BPS as a subcutaneous injection

INTRAVESICAL AND INTRAMURAL BLADDER TREATMENT

Intravesical therapies are treatments where the medication is applied directly to the bladder or bladder wall by means of instillation. Intramural treatment is when the treatment is injected into the bladder wall. This means that the medication immediately reaches the right place and far higher concentrations come into contact with the bladder wall than in the case of oral medication. Adverse effects are limited due to the fact that short treatment times mean that there is relatively little absorption of the drug from the bladder into the bloodstream. This is one of the main advantages of bladder instillations. A disadvantage is that the patient has to be catheterized to allow the bladder to be emptied and the medication to be instilled. There is always a risk of infection occurring during catheterization, but these days this is relatively minor bearing in mind the high quality, sterile material that is used. Antibiotics are sometimes given – either orally or intravesically - simultaneously with the instillation as a preventive measure. When catheterizing at home, scrupulously careful hygiene – e.g. thorough cleansing of the area from front to back in women, using disposable plastic gloves etc. – can help prevent any risk of infection.

Catheterization can be an uncomfortable or even painful procedure for IC/BPS patients. Application of lidocaine gel in the urethra before insertion of the catheter may help to reduce urethral pain on catheterization.

A new **minimally invasive device for intravesical instillation** has been invented in Budapest in the form of a urological syringe adapter designed to inject solutions directly into the bladder through the urethra. It is a potential solution for catheter-free instillation in patients when catheter use is too

painful due to urethral pain. Currently being trialled, it is known as the MID-ii® and also as the laludapter®.

Drugs used for intravesical instillation can be used alone or as a cocktail in which several active ingredients are combined, including for example any of the following: a steroid, an antibiotic, DMSO, heparin, PPS, a painkiller such as lidocaine combined with sodium bicarbonate (the bicarbonate of sodium alkalizes the lidocaine and allows it to be absorbed), hyaluronic acid or chondroitin sulfate. A course of treatment may involve just a few instillations or numerous applications.

The so-called **anaesthetic cocktails** for immediate pain relief and as a rescue treatment usually comprise alkalized lidocaine with or without heparin. The effect can last for several days or even weeks. In some patients, lidocaine with or without alkalization can occasionally briefly cause systemic side effects.

Some of the drugs used for instillation are aimed at replenishment of a suspected deficit in the GAG (glycosaminoglycan) layer of the bladder. This is the protective layer of the surface of the bladder wall which protects the underlying layers of the bladder wall from penetration by toxic or irritative elements in the urine and by infection. This GAG layer is believed to be impaired in some patients with IC/BPS (and other bladder disorders including radiation cystitis).

Most of the fluids used for instillation need to remain in the bladder for 15-60 minutes to achieve an adequate effect. The time varies depending on the drug used.

Administration of the instillation can take place at the urology clinic, but if instillations are necessary one or more times a week, or if the cost is not reimbursed, the patient can be taught self-catheterization to be able to administer the drug at home. Many patients find this an advantage, but it requires good eyesight and good hand/eye coordination since the patient has to insert the catheter using a mirror reflection for guidance. Not all patients can manage this. The most patient-friendly method is treatment available in a pre-filled syringe.

DRUGS USED FOR BLADDER INSTILLATION (ALPHABETICAL ORDER)

Antibiotic: an antibiotic is sometimes added to bladder cocktails to help prevent any bladder infection due to catheterization. Alternatively, a single preventive oral dose can be taken. However, long-term use of antibiotics should be avoided because of the risk of resistance building up.

BCG (Bacillus Calmette-Guérin), originally a vaccine used to provide protection against tuberculosis, has been used for some time to treat different types of bladder cancer. BCG causes an immune response leading to the production of a variety of cytokines. Some of these cytokines have antiangiogenic activity whereby they inhibit the formation of blood vessels needed for tumours to grow. Despite some positive results in the past with IC/BPS patients, recent studies have indicated that it is probably ineffective in IC/BPS and is **not recommended**.

Bupivacaine is a local anaesthetic drug that can provide long acting local pain control in the bladder. It is sometimes used in patients who do not respond to intravesical lidocaine. It is more lipophilic and potent than lidocaine. (20 ml 0.5% bupivacaine). Can be used alone or in cocktails. Sometimes combined with heparin (10,000 IU of heparin, 10 ml of bupivacaine). Studies have also shown it to be effective in treating bladder spasms.

Chondroitin sulphate, a GAG-replenishment treatment, is a substance that occurs naturally in the bladder GAG layer. Treatment with chondroitin sulphate, available in different strengths under

several brand names including Uracyst® (2.0%) and Gepan® Instill (0.2%), is believed to replenish deficient chondroitin sulfate in the GAG barrier and to help prevent irritants in the urine from penetrating the bladder wall. Studies have indicated that it is safe, effective and well-tolerated. It can be used alone or in combinations. It may help not only IC/BPS but also radiation cystitis, chemically induced cystitis, overactive bladder and chronic bacterial cystitis.

Corticosteroids can also be used intravesically, either alone or in a cocktail.

Disodium cromoglycate is a substance that inhibits mast cells. Urologists have used this drug for some time as a bladder instillation with varying success. However, any improvement in symptoms is generally short-lived and the symptoms soon return.

DMSO (dimethylsulfoxide) is one of the most commonly used drugs for bladder instillation and is one of only two drugs for IC/BPS approved by the American Food and Drug Administration (FDA). It is often the first drug to be tried because it has a number of properties that are of importance to IC/BPS. It is believed to be anti-inflammatory, analgesic and relaxes the bladder muscles. The symptoms are sometimes exacerbated for a few days following treatment but hopefully then show an improvement. The full effect of treatment may not be seen for several weeks. In some patients the symptoms may worsen after the first few treatments. A little of the DMSO penetrates the bladder wall and passes via the lungs into the breath, giving rise to the well-known garlic-like taste and odour coming from the breath and skin for up to 72 hours after treatment. DMSO can be combined with other drugs as a cocktail, for example with heparin and bicarbonate. Studies have shown that patients, who have undergone a period of treatment with DMSO instillations and have responded well, maintain their improvement if they then receive a monthly maintenance therapy of heparin instillations. This development looks promising for patients who respond favourably to DMSO, although symptoms may worsen in some patients.

The DMSO cocktail (6-8 weekly cycles):

- 50% DMSO 50cc
- Triamcinolone 40mg
- Heparin sulfate 10,000-20,000 IU
- Sodium bicarbonate 44 meq
- +/- Gentamicin

Source: Robert Moldwin MD, IC & Related Conditions: Practical Management Strategies AUA Annual Meeting Chicago 29/4/2009

Doxorubicin (Adriamycin®) is a chemotherapy drug used in the treatment of cancer. It has been used experimentally with some positive results as a bladder instillation for IC patients with severe Hunner lesion.

Heparin is a drug commonly used as an anticoagulant (a blood thinner to inhibit blood clotting). It is also believed to have an anti-inflammatory effect on the cell layers on the surface of the bladder wall and may temporarily repair the so-called GAG layer. Like PPS, it can take 2-3 months before it produces any effect. It can be used alone or in cocktails. Relatively inexpensive and widely available.

Hyaluronic acid, also called Sodium hyaluronate or hyaluronan, a GAG-replenishment treatment, is one of the naturally occurring substances in the glycosaminoglycan or GAG layer of the bladder wall and all connective tissues. Like chondroitin sulphate, heparin and PPS, it is believed to temporarily repair the damaged GAG layer and thereby reduce the pain, urgency and frequency of IC/BPS. Sodium hyaluronate is reported to be well tolerated. Cystistat® has been registered for the temporary replacement of the GAG layer in the bladder and is commercially available in about 20 countries. Another hyaluronate treatment brand is Hyacyst®. European studies have shown positive

results with a reduction in pain and some reduction in frequency. This treatment is also used for other (painful) bladder conditions including radiation cystitis, chemically induced cystitis, overactive bladder and chronic bacterial cystitis. Studies have indicated that selection of patients who are likely to respond to this treatment can be improved by using the modified potassium sensitivity test.

Hyaluronate acid + chondroitin sulphate are also available combined in a single intravesical treatment and this has shown promising results so far. Brand names include iAluril®.

Lidocaine (local anaesthetic) is used for pain treatment, sometimes with only sodium bicarbonate (to alkalize the lidocaine) or in combination with other drugs such as heparin in a bladder instillation cocktail aimed at multi-modal treatment. It can also be used as a rescue treatment for the relief of severe pain in a flare. Alkalinized lidocaine is also used in the anaesthetic challenge test to assess whether the pain is actually coming from the bladder.

Studies have shown that lidocaine needs to be alkalized with sodium bicarbonate otherwise it does not get absorbed. There have been reports of improved absorption using electromotive drug administration (EMDA) of lidocaine to anaesthetise the bladder. A new drug delivery system for lidocaine is currently being investigated (LiRIS® or lidocaine releasing intravesical system). This device looks like a tiny pretzel, is inserted cystoscopically and releases lidocaine slowly into the bladder over a given period of time. Still under trial.

Proprietary brands under development:

- **URG101:** A new investigational, proprietary bladder instillation using lidocaine to reduce the pain, urge and muscle spasm and heparin to coat the bladder wall.
- **PSD597** (intravesical alkalized lidocaine) has been shown to be effective in providing sustained symptom improvement. It is considered to be safe and well-tolerated. Further studies are in the pipeline.

Recipes for intravesical anaesthetic therapy:

- 2% Lidocaine jelly
- 0.5% Marcaine
- 10,000-20,000 IU Heparin Sulfate
- 40 mg Triamcinolone
- Treatments administered 2-3 times per week

Source: Robert Moldwin MD, Professor of Urology, Hofstra North Shore-LIJ School of Medicine, Urologic Infectious/ Inflammatory Diseases, Director of the Pelvic Pain Center, The Arthur Smith Institute for Urology of the North Shore-LIJ Health System. USA, infectious/inflammatory diseases, Smith Institute of Urology, Director Interstitial Cystitis Center, North Shore-LIJ Health System. Associate Professor, Albert Einstein College of Medicine, New York. IC & Related Conditions: Practical Management Strategies AUA Annual Meeting Chicago 29/4/2009

0.5% bupivacaine (Marcaine, 20 mL)
 10,000 IU heparin (10 mL)
 100 mg hydrocortisone (5 mL of normal saline)
 40 mL sodium bicarbonate 48 mmol

Source: Kristene Whitmore MD, Professor of Urology, Chair of Urology and Female Pelvic Medicine and Reconstructive Surgery, Drexel University College of Medicine, Philadelphia, PA, USA

Liposomes are literally globules of fat. When used intravesically, they are believed to help the absorption of other drugs they are combined with. Current being investigated are liposomes with botulinum toxin. A further hypothesis is that they may be of value when used alone by creating a temporary barrier film over the bladder lining that can prevent penetration by irritant substances in the urine and also promote wound healing. A study showed a decrease in pain and urgency. Still experimental but looking promising for IC/BPS for use in different ways.

Pentosan polysulfate sodium is also used as a bladder instillation and in this form appears to have an even better effect than the oral form and is less likely to have side effects. Its main properties are believed to be strengthening the GAG layer, reduction of pain and anti-inflammatory effects. Since it does not appear to be very effective against other IC/BPS symptoms, it is generally used in a cocktail with other agents.

Oxybutynin chloride, an older drug commonly used for overactive bladder, is also sometimes used as bladder instillation for IC/BPS, often in cocktails. It reduces the frequent urge to urinate by increasing bladder capacity and controlling bladder spasms. With intravesical treatment, side effects are less likely than with the oral form.

RDP58: an investigational immunomodulatory peptide with anti-inflammatory effects currently being investigated as a potential intravesical treatment for autoimmune-associated bladder inflammation such as IC/BPS. A study indicated that it inhibits cell-mediated bladder inflammation in an autoimmune cystitis model.

Resiniferatoxin, one of the so-called vanilloids, is an intravesical treatment with a desensitising effect that has been used to treat overactive bladder and hypersensitive painful bladder. Many times more potent as a pain reliever than capsaicin (an extract of chilli peppers), it is said to cause far less burning and irritation. Studies with RTX® in the United States failed to show any positive results for IC/BPS patients, although studies elsewhere were a little more positive and it does appear to help a few patients. A new, more stable form is now available and may prove more effective.

Tacrolimus is an immunosuppressive agent used to prevent rejection of transplanted organs and is currently being investigated experimentally as an intravesical therapy for IC/BPS patients. As an immunosuppressive drug, tacrolimus could be used in treating autoimmune diseases. While one recent study showed that it may have many side effects, results in India have shown some success. The most common side effects shown in studies are tremor, headache, abdominal pain and pruritus.

DRUGS USED FOR INTRAMURAL BLADDER INJECTION

Botulinum toxin A, a neurotoxin produced by bacterium clostridium, is the world's most potent biological toxin known to man and has generated a flurry of excitement in the urological world in recent years as a treatment for urethral and bladder dysfunction. Botox is injected into the bladder: submucosal injections preferably into the trigone. The effect wears off after some months, even up to a year, but can then be repeated. Researchers are currently carrying out trials for IC/BPS patients. The drug works by reducing sensation and reducing the strength of the bladder contractions. Studies have produced conflicting results with some trial results negative, some positive. Side effects have included urinary retention which may last several months until the effect of the treatment wears off. Recent studies have indicated that there is less risk of retention when injected into the trigone. More trials are needed to get a really clear picture.

This is still experimental in IC/BPS but may help some patients. A study from Taiwan found that this treatment is effective in non-lesion bladder pain syndrome but not in patients with lesions.

Different types of botulinum toxin now on the market.

The various botulinum toxins possess individual potencies, and care is required to assure proper use and avoid medication errors. Recent changes to the established drug names by the FDA were intended to reinforce these differences and prevent medication errors as the dosage of the different brands is not equivalent.

The products include the following:

Botulinum toxin A

Onabotulinumtoxin A (onabotA: Botox®)
 Abobotulinumtoxin A (abobotA: Dysport®)
 Incobotulinumtoxin A (incobotA: Xeomin®)

Botulinum toxin B

Rimabotulinumtoxin B (rimabot B: Myobloc®)

Onabotulinumtoxin A has recently been studied in combination with hydrodistension.

Triamcinolone submucosal injection has been studied for the treatment of **Hunner lesion** with very good results. Under general anaesthesia, triamcinolone (40mg/cc) was injected with an endoscopic needle in volumes ranging from 5-10 cc (depending on the number and size of the lesions) into the submucosal space of the centre and periphery of lesion(s). It appeared to be well-tolerated in 66% of patients with Hunner lesion.

Gene-gun therapy, experimental therapy aimed at suppressing bladder pain responses with narcotics, is being studied for IC/BPS using a gene-gun method of transfer into the peripheral nerves of the bladder.

EMDA – ELECTROMOTIVE DRUG ADMINISTRATION

EMDA is a method of accelerated delivery of drugs deep into the bladder using a small amount of electricity. It appears to be a safe and effective approach to treating IC/BPS. Studies have shown it to achieve significant prolongation and enhancement of symptom improvement compared to normal instillation of drugs.

HYPERBARIC OXYGENATION

Studies into Hyperbaric Oxygenation (HBO) have produced encouraging results with IC/BPS patients. The patient is placed in a pressurized treatment chamber and breathes 100% oxygen. This is a treatment that has already been successfully used for patients with radiation cystitis, appears to be safe and has shown moderately good results with a small number of IC/BPS patients, but is expensive and has limited availability.

SURGERY

Surgery includes surgical interventions on the nervous system (neuromodulation) and surgery on the bladder itself.

Laser ablation, electrocoagulation or transurethral resection (TUR) for Hunner lesion

These forms of treatment are reserved for patients with Hunner lesion and are used to treat the lesions. They have a temporarily alleviating effect on the pain for several months or even several years and can be repeated when necessary. While good symptom improvement has been seen in studies with neodymium Yag-laser treatment, it is essential for patients to be treated by very experienced surgeons since this therapy carries the risk of complications such as accidental bowel perforation in less experienced hands.

TUR has been shown to lead to considerable improvement in both pain and frequency in many lesion patients.

Bladder hydrodistension or inflation (stretching)

Bladder hydrodistension or stretching is not only used for diagnostic purposes but also sometimes for the treatment of IC/BPS in selected patients. Distension of the bladder has been used to treat IC/BPS patients since 1930 with varying results. Distension is carried out by filling the bladder above its known capacity. A well-known procedure is the Helmstein method where, under epidural anaesthesia, the bladder is stretched for three to six hours by means of a balloon inserted in the bladder. Distension can cause temporary exacerbation of symptoms in IC/BPS patients for a few days. Results of this procedure are variable and the duration of the improvement unpredictable. It is currently thought to have a beneficial effect in 30%-50% of patients. Many patients report that their symptoms return within three months. Regarding the role and value of hydrodistension as a therapy, recent studies indicate that it may improve symptoms in only a minority of patients. Hydrodistension should be undertaken only with the greatest caution in patients where Hunner lesions are known or suspected to be present due to the high risk of bladder perforation and subsequent bleeding.

Neuromodulation / electrostimulation (nerve stimulation)

An important development in the field of urology is neuromodulation of the sacral or pudendal nerve roots for the treatment of bladder dysfunction and urinary incontinence. Neuromodulation is a potentially important form of treatment for selected patients but is still an expensive option which is neither available nor affordable in many countries. The principle of neuromodulation is not a new one. Electric stimulation has been used as a pain therapy since the nineteen sixties (e.g. TENS, see below). It works by reconditioning the nerves that control bladder function. Unwanted contractions of the bladder are inhibited and normal bladder function is restored.

TENS (Transcutaneous Electrical Nerve Stimulation)

The oldest form of nerve stimulation is TENS. This is non-invasive and does not require surgery. With TENS, mild electric pulses are transmitted into the patient's body by placing electrode pads on the suprapubic region or the lower back. Electric stimulation is generated by a small portable unit. Many IC/BPS patients in different countries still use TENS as a form of (supplementary) pain control. Scientists believe that by stimulating nerve fibres with TENS, pain signals transmitted to the brain are blocked. TENS is also believed to increase the body's own natural pain-killing chemicals known as endorphins. TENS can be used at home by patients as pain relief in combination with other standard treatments. It is non-invasive, inexpensive, has no serious side effects and may help some patients.

Percutaneous Tibial Nerve Stimulation (PTNS), is a neuromodulation system intended to treat patients suffering from overactive bladder and associated symptoms of urinary urgency, urinary frequency and urgency incontinence that can be delivered in an outpatient setting. PTNS is a simple form of nerve stimulation via a fine needle electrode inserted near the tibial nerve located near the ankle. Electrical stimulation is applied using a low voltage external pulse generator. This sends a mild electric current via the posterior tibial nerve to the sacral nerves that control the bladder and pelvic floor function. This form of stimulation is carried out for 30-minute sessions once a week as the patient sits comfortably and shown very positive results in OAB patients, especially those for who may have tried other therapies or drugs that were not effective. After 12 sessions, if the patient's symptoms have subsided or improved, the patient may need occasional on-going therapy to sustain their symptom improvement. In clinical studies this averages about 1/month.

Interstim® Sacral Nerve Stimulation (SNS) is a neuromodulation option for patients who have failed to respond to standard treatments and have long-standing, invalidating symptoms. This therapy is used for an overactive bladder, i.e. an uncontrollable, frequent need to urinate and/or urgency incontinence, with either a non-neurogenic or neurogenic cause. It is also used for patients with a so-called "lazy bladder" who are unable to (fully) empty their bladder (retention). This treatment has been used to treat the above-mentioned symptoms for more than 10 years now and has a long-term success rate of about 70% in patients with a positive Percutaneous Test Evaluation. In recent years,

experience has also been acquired in the treatment of IC/BPS patients and encouraging results have been published.

Pudendal Nerve Stimulation (PNS) is performed in a similar way. In a study with SNS and PNS in 2007, most of the IC/BPS patients in the study showed a preference for PNS and this could be a potential path for the future for selected patients. Two phases: test stimulation and implantation: During the test stimulation procedure, a temporary electrode is implanted low down in the patient's back. This electrode is connected to an external stimulator. During the test period (3 to 7 days), the effect of the stimulation is recorded daily in a journal. The decision to go ahead and carry out the implant is based on the information recorded in the journal before and during the test stimulation and on the patient's experiences. A definitive implant is suggested if there is at least a 50% improvement in the patient's symptoms. When definitive implantation takes place, a permanent electrode is implanted in the lower back region and connected to a kind of pacemaker (battery-powered pulse generator) that supplies a continuous, very low/mild current to the relevant nerves. It is still investigational.

Surgery on the bladder and lower urinary tract

In some IC/BPS patients, the problems with their bladder are so extreme that surgery remains the only option. This is not something to be undertaken lightly since IC/BPS is a complex disease and surgery may lead to other complications. It is therefore important for patients to understand exactly what is involved and the potential side effects and consequences.

One problem that may occasionally occur following surgery and removal of the urinary bladder is "phantom pain". Even when the old, diseased bladder has gone, pain may still continue to be felt. Recent studies have indicated that this may be caused by changes in the pain centres in the brain and spinal cord.

Surgery includes bladder augmentation, urinary diversion, and partial or complete cystectomy and should only be undertaken by experienced surgeons.

Irreversible surgical options should be considered only when all conservative treatment has failed. The patient should be thoroughly informed about all aspects of the surgery and understand the consequences and potential side effects of surgery.

Bladder augmentation cystoplasty

Also known as a clam cystoplasty, this is a procedure where the patient's own bladder is enlarged through the addition of a piece of the patient's intestine. This may be taken from the patient's small or large intestine or the stomach lining. This has not been an unmitigated success in the majority of IC/BPS patients since the pain, urgency and frequency may either remain or return, particularly in patients with a large capacity under anaesthesia. If pain plays an important role in the patient's symptoms, this will not necessarily be reduced after the augmentation procedure.

Following augmentation surgery, patients may be unable to urinate independently and need to use a catheter in order to empty the bladder (intermittent self-catheterization). Regular self-catheterization may be a painful procedure for IC/BPS patients due to the hypersensitivity of the urethra and bladder base. There is also a greater risk of urinary tract infections because intestinal mucosa is easily colonised by bacteria, while there are also likely to be changes in the way the bowel functions. Nevertheless, it does sometimes work or is chosen as a temporary measure before taking the final step to completely remove the bladder (cystectomy). Bladder augmentation is more effective in patients with a very small, shrunken bladder where pain plays a more minor role than frequency.

Bladder removal, urinary diversion and urostomy

In cases where a patient has very severe intolerable pain or pain and a small bladder capacity and has failed to respond to any other treatment, urinary diversion may be necessary with or without complete cystectomy. This involves diverting the urine flow to a new opening in the abdomen known as a urinary stoma or urostomy. Urine normally passes from the kidneys to the bladder via two ureters. In a urinary diversion, these two ureters are connected to a segment of intestine. Sometimes the old bladder is left in place. Cystectomy is complete surgical removal of the urinary bladder. Some surgeons believe that in the case of IC/BPS patients it is preferable for every piece of the bladder and urethra to be removed in a cystectomy. Other surgeons leave the bladder in place, while diverting the urine. Results vary greatly from patient to patient and there is no guarantee of complete success.

Ileal conduit urostomy

This is a method where the urine is diverted to an external disposable bag attached to the outside of the body, for example the Bricker technique. A piece of tube-shaped intestine is removed from the intestines. The ureters that normally carry urine to the bladder are now attached to this at one end while the other end is formed into a “stoma” opening on the surface of the abdomen. A disposal, external bag can be attached to the stoma to collect the urine.

Continent diversion urostomy

A continent diversion, such as the Kock or Indiana pouch, consists of an internal reservoir or pouch (made from a section of intestine) serving as a new bladder where urine can be stored and drained at specific intervals through a stoma opening on the surface of the abdomen using a catheter. Although the continent diversion with its internal pouch and catheterisable stoma on the outside may be more attractive to the patient from a cosmetic point of view, it may lead to pouch complications with recurrence of pain and inflammation, nipple valve failure and leakage in IC/BPS patients.

A continent stoma is also considered to be less suitable for patients who also have kidney dysfunction.

Any patient with a continent stoma must be physically able to undertake the regular catheterization of the stoma.

Neobladder

An alternative method is a bladder substitute continent diversion, with a new bladder (neobladder) formed from segments of intestine at the site of the old bladder and using the old urethra to empty the bladder. This will have to be done with a catheter.

Urostomy associations will be able to provide patients with detailed information concerning the different surgical options and stoma care.

Denervation not recommended

Peripheral/sympathetic/parasympathetic denervation is **not recommended** for IC/BPS.

Catheterization (indwelling) for surgery

When undergoing surgery, including non-urological surgery, IC/BPS patients may need to be catheterized for several days or longer, using an indwelling catheter which is secured in place with a small inflatable balloon inside the bladder, preventing the catheter from slipping out of the urethra. An indwelling catheter may be left in place for a short or longer time. The urine is usually collected in a drainage bag.

An indwelling catheter can cause intense irritation and pain in the bladder of an IC/BPS patient. One solution is to use a 100% silicone catheter and only partly inflate the balloon.

TREATMENT FOR HUNNER LESIONS (formerly known as Hunner’s ulcers)

Hunner lesions, historically known as Hunner's ulcers (even though ulcer is not the correct medical description), are also known as Classic IC and are today considered to be a separate disease from non-lesion IC/BPS. In recent decades, Hunner lesions have been diagnosed with cystoscopy plus hydrodistension. However, office cystoscopy without hydrodistension is sometimes carried out instead. Nevertheless, while some types of lesion can be seen without hydrodistension, others may be difficult to detect without hydrodistension. Narrow Band Imaging is a relatively new way of detecting lesions, currently used in Japan.

Pain in the bladder caused by lesions can improve dramatically when treated with fulguration/electrocoagulation, laser (burning out and sealing the lesion) or resection (surgical removal of the lesion). This treatment needs to be periodically repeated as and when the pain returns. This may be after a few months or after several years. A promising treatment for Hunner lesions is submucosal injection of the corticosteroid triamcinolone.

COMPLEMENTARY & ALTERNATIVE MEDICINE (CAM)

What is Complementary & Alternative Medicine? The American NIH National Center for Complementary and Alternative Medicine (NCCAM) explains on its website (<http://nccam.nih.gov>) what is meant by the terms complementary and alternative, as summarised below.

- Complementary: generally refers to using a non-mainstream approach **together with** conventional medicine.
- Alternative: refers to using a non-mainstream approach **in place of** conventional medicine. (see fact sheet <https://nccih.nih.gov/health/integrative-health>).

However, the CAM concept should be seen as fluid and continually evolving since many treatments once considered alternative have now shifted into the complementary category (e.g. acupuncture), while some former complementary approaches have now become more or less mainstream (e.g. cognitive-behavioural therapy).

There are many complementary therapies and self-help possibilities that may alleviate symptoms, relax the patient and help to achieve a better quality of life. Because of the limited effectiveness of traditional treatment in many IC/BPS patients, these patients tend to seek other non-medical forms of therapy from which some patients experience benefit and relief. One of the possible reasons may be because this type of therapy involves relaxed interaction between the practitioner and patient, while by contrast conventional medicine nowadays often resembles a fast-moving production line with little time for communication with patients. This kind of therapy can often help a patient to achieve relaxation of body and mind, with progressive relaxation of tense and tender pelvic floor muscles, which may help in reducing pain. Any therapy where the patient can relax on a couch and have the time to discuss their symptoms and the impact of these symptoms on their life is likely to have a stress-reducing effect.

Pelvic floor dysfunction is an important but under-recognised factor in both IC/BPS and Chronic Prostatitis (CP). Basic therapy should include: no pushing or straining with urination, avoid constipation, warm baths twice a day, skeletal muscle relaxants, physical therapy.

Complementary approaches include biofeedback which helps patients gain awareness of and greater control over muscles that cause pain, hypnotherapy, trigger-point therapy, myofascial pain therapy, pelvic floor re-education, acupuncture and herbal supplements.

Relaxation techniques of any kind can help in reducing stress, including yoga, Tai Chi, meditation, breathing exercises (slow diaphragmatic breathing), regular exercise, walking (even short distances), swimming, warm baths, hydrotherapy, guided imagery.

However, in order to achieve optimum results from either physical therapy or relaxation therapy, every endeavour should be made to bring the symptoms and particularly the pain aspect under control through traditional medical therapy.

Kegel exercises are not recommended for IC/BPS patients, nor are pelvic floor strengthening exercises.

Bladder training

Bladder training or re-education (timed voiding, gradually increasing the voiding interval) is likely to work better in selected patients where urgency/frequency predominates. Pain limits the possibility of retraining the bladder until the pain has been brought under control. Once pain control has been achieved, the bladder can be re-educated by very slowly increasing the period of time between voids, thereby reducing frequency and increasing bladder capacity. But if the patient has a strong urgency sensation, this may be difficult and results short-lasting. In any case, it takes some months before results are seen. Bladder training should be done under medical supervision. There is little point in trying bladder training in patients with a shrunken, contracted, fibrotic bladder and it is not recommended for patients with pain.

Voiding diaries

Voiding diaries or charts, today often available in electronic form, can provide both the patient and the doctor with an overview of the number of voids per 24 hours and if required also the volume voided. A recently designed voiding chart also includes the bladder sensation assessed by the patient on a scale of 0-5. The results of a voiding chart are likely to vary if it is a patient who experiences the strongest symptoms in the form of flares. Where frequency is concerned, a patient's drinking habits play an important role since a patient drinking 2 or more litres a day is going to have a much higher frequency than a patient drinking less than half a litre a day. The level of perspiration is also an important factor in urinary frequency and this will partly depend on the climate.

Voiding diaries (with number of voids only, per day and night) can also be used to monitor the success of treatment from time to time.

Useful overview of current treatment and investigational drugs:
Investigational drugs for bladder pain syndrome (BPS) interstitial Cystitis (IC).
Chuang YC, Chermansky C, Kashyap M, Tyagi P. Expert Opin Investig Drugs.
2016 May;25(5):521-9. doi: 0.1517/13543784.2016.1162290. Epub 2016 Mar
22.

CHAPTER 6 - IC/BPS & ASSOCIATED DISORDERS

Many patients with IC/BPS also have one or more non-bladder conditions or symptoms in addition to their bladder problem, including other chronic pain syndromes, allergy/hypersensitivity, chronic fatigue, rheumatic/autoimmune diseases, gastrointestinal or gastroesophageal disorders and vulvar pain conditions, as shown by studies and patient surveys.

Since IC/BPS patients are generally treated by a urologist, some of these associated disorders may go undiagnosed and untreated. This underlines the need for a multi-disciplinary approach. Associated disorders should always be taken into account when treating IC/BPS and often make treatment very challenging.

Associated disorders (also known as comorbidities or non-bladder conditions)

A number of survey studies have indicated that some diseases and disorders appear to occur more frequently in IC patients than in the general population. These are known as associated disorders or comorbidities or non-bladder conditions and may be grouped as follows:

- allergies or intolerances (including multiple chemical and drug intolerance),
- different chronic pain and fatigue syndromes,
- systemic autoimmune diseases (such as Lupus (SLE), Sjögren's syndrome or rheumatoid arthritis),
- gastrointestinal or gastroesophageal disorders
- neurological disorders.

These can include for example the following disorders:

- allergy/hypersensitivity,
- anxiety
- chronic fatigue (syndrome)
- depression
- fibromyalgia,
- gastro-intestinal and gastro-esophageal disorders
- interstitial nephritis (e.g. distal renal tubular acidosis – dRTA)
- low back pain
- migraine/headaches
- rheumatoid arthritis, arthritis
- Sjögren's syndrome
- systemic lupus erythematosus
- temporomandibular joint disorder
- vulvodynia

The possible relationship between IC/BPS and other disorders that may co-exist with IC/BPS, and why these disorders should occur alongside each other in the same patient, is still unknown and is currently the subject of much research.

Since diagnosed IC/BPS patients are generally treated by either a urologist or urogynaecologist, some of these associated disorders may go unrecognised, undiagnosed and untreated. This underlines the need for a **multi-disciplinary approach**.

Both the doctors treating IC/BPS patients and the patients themselves should be on the alert for other symptoms that may indicate another disorder since in some cases it might change the approach to treatment of the bladder disorder. See table 3.

Autoimmune disease and IC/BPS

One of the many theories concerning IC/BPS is that it might itself be an autoimmune disease. Rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome and thyroid disorders are examples of autoimmune diseases. In autoimmune diseases, the immune system attacks the patient's own body. Some autoimmune diseases may be "organ specific", i.e. they attack one specific organ in the body (for example thyroid disorders). Others may be "generalized" or "systemic": this means that they attack many different organs and systems throughout the body, including the urinary tract. Patients who have both a diagnosed autoimmune disease and IC/BPS should be sure to inform their specialists of this fact, particularly if the autoimmune disease is diagnosed after the IC/BPS has been diagnosed and the urologist is unaware of this, since this might mean using different types of medication to treat the IC/BPS (see below systemic treatment).

A problem with IC/BPS patients with symptoms indicative of autoimmune disease is that laboratory tests may reveal few or no abnormalities. The patients often do not quite fulfil all the criteria of any single specific disease. While strict criteria are created for the purpose of research, they are all too frequently applied clinically too. The result is that many sick patients may still be going undiagnosed and untreated. If an autoimmune disease is suspected, patients should be referred to an internist, immunologist or rheumatologist. It may also be necessary to see a gastroenterologist or neurologist.

Systemic treatment

Some IC/BPS patients who display symptoms of autoimmune diseases in addition to IC/BPS may benefit from "systemic" treatment (i.e. treatment of the whole body with one medication), for example the antimalarial hydroxychloroquine and the anti-inflammatory sulphasalazine (commonly used to treat inflammatory bowel disease and rheumatic diseases) or corticosteroids such as prednisolone, dexamethasone or hydrocortisone. Some patients have reported a substantial improvement in their IC/BPS symptoms through this treatment. However, here too treatment is highly individual and every patient is different. Side effects could be problematic in some patients.

Multiple pain syndromes

In recent years, attention has been focused on the fact that some IC/BPS patients appear to suffer from not simply multiple disorders, but also multiple pain syndromes, affecting different parts of the body and not only the pelvic organs. Sometimes referred to as chronic overlapping pain conditions (COPCs). Some patients suffer from a variety of combinations of pain conditions, for example: IC/BPS, chronic prostatitis (CP/CPSP), irritable bowel syndrome, vulvodynia, fibromyalgia, migraine, temporomandibular disorder, and other painful disorders. It is still unclear why this occurs in some IC/BPS patients and not in others. The NIH/NIDDK **Multidisciplinary Approach to the Study of Pelvic Pain (MAPP) Network** is currently studying these pain syndromes together with IC/BPS and CP/CPSP to see what they have in common and what the risk factors are and will endeavour to characterize patients into types (phenotyping) for treatment purposes. This is a large-scale ongoing study that started in 2008.

Many pain theories

Pain researchers' theories concerning the occurrence of multiple pain syndromes currently include central nervous system involvement, damage or inflammation in one organ of the body affecting another organ or system either due to central nervous system processing or to so-called cross-sensitization or cross-talk with inflammation in one organ causing inflammation in another, abnormalities of autonomic function and most recently limbic dysfunction. IC/BPS patients may indeed suffer from widespread pain. Much research is currently being focused on changes in the

brain caused by chronic pain. Furthermore, bearing in mind the variations in bladder pain felt by women during their menstrual cycle, it is also theorized that there may be hormonal involvement in pain perception in these women.

A brief look at a few associated disorders

Allergy/hypersensitivity: Many IC/BPS patients suffer from allergy/hypersensitivity, including food, chemicals and drugs. Allergies can affect the skin, airways and sometimes organs. Examples of allergy include asthma, rhinitis, urticaria (nettle-rash), eczema and anaphylaxis. True allergies can be identified by allergy tests. In some cases, patients receiving antihistamines for their allergy find that this treatment also has a beneficial effect on their bladder symptoms.

However, not all hypersensitivity reactions are true allergy and may in fact be a question of non-allergic hypersensitivity, often known as intolerance or other variations. The problem with this non-allergic hypersensitivity is that reactions to drugs may be unpredictable and variable, are often a question of trial and error and largely impossible to “diagnose” by standard allergy tests. Non-allergic hypersensitivity is still a relatively unexplored, unresearched field and particularly so in relation to the drug intolerance (often multiple drug intolerance) found in some IC/BPS patients. Some IC/BPS patients may also have multiple chemical intolerance and feel sick, dizzy and faint if there are chemicals in the air or if perfumed products or chemicals touch their skin. At present, it is unknown why some IC/BPS patients have these problems and others not. It is, however, interesting to note that multiple drug intolerance and multiple chemical intolerance are also found typically in patients with fibromyalgia.

Drug intolerance may affect, for example, cognitive functioning, eyesight and balance and cause dizziness, faintness, headache, general malaise, fatigue, drowsiness or sedation.

Patients with drug intolerance often respond better to intravesical treatment for their IC/BPS where less of the drug is absorbed into the system.

Finding a solution to drug intolerance would make it considerably easier to find an adequate treatment for many patients, thereby relieving the anxiety caused by multiple drug intolerance and greatly improving quality of life. And of course we should not forget that expensive drugs are being thrown away.

Chronic non-bacterial prostatitis: Chronic non-bacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common form of prostatitis. The older term prostatodynia is also sometimes used to describe this painful prostate condition. New terms include prostate pain syndrome and perineal pain. Unlike acute or chronic bacterial prostatitis, it is not caused by any identifiable infection and therefore does not respond to treatment with antibiotics. It may be inflammatory or non-inflammatory. While its cause is unknown, one theory that has been suggested is that it could be of autoimmune origin. CP can sometimes be mistakenly diagnosed when the patient in fact has IC/BPS. For further detailed information, see: www.prostatitis.org

Depression is experienced by many people in the general population, either occasionally or persistently but may particularly occur in patients with chronic disorders such as IC/BPS. Sometimes it is a question of being temporarily “down” or “moody” or “sad” or unable to cope, but sometimes it is more serious and needs treatment and professional counselling. Some patients may not actually realize that they are suffering from depression and this may partly be due to confusing usage of the word “depression”. People so often say that something that has occurred has made them “so depressed”, when in fact they mean that they are upset or sad or shocked about a specific incident. Under normal circumstances, patients will adjust to the situation and soon recover. However, in cases of true depression, the sad or down feeling will persist. There may be multiple effects: weight can go up or down, patients may sleep too much or too little, may feel tired all the time and have no energy, have feelings of guilt, feel worthless, experience confusion or forgetfulness (*cognitive*

impairment), have suicidal thoughts. Depression can make it impossible to work, study and cope with or enjoy everyday life. While depression may be caused by psychiatric disorders, it may also form part of a syndrome of symptoms in chronic diseases, as has been documented in systemic lupus erythematosus, and may potentially occur in any disease with a neurological component including pain syndromes. “Mood” disorders are caused by chemical imbalances in the brain. This may be caused by an illness, by hormone imbalance, even by certain medications. Treatment may be aimed at changing the chemical imbalances in the brain.

In IC/BPS patients, it may be a question of a temporary inability to cope which can be helped by good support and a sympathetic approach from their doctor, by a patient support group, by support in the home environment. If more serious, it should be treated with medication combined with counselling.

Depression in IC/BPS patients may be combined with anxiety and/or panic attacks and this can respond to treatment. Above all, patients should not be afraid or feel guilty about admitting to their doctor that they are suffering from depression. Professional help should always be sought for suicidal patients.

Further reading:

The National Institutes of health have a useful booklet on depression online:

<http://www.nimh.nih.gov/health/publications/depression/complete-index.shtml>

and also a specialised leaflet on Men and Depression to be downloaded at:

<http://www.nimh.nih.gov/health/publications/men-and-depression/complete-index.shtml>.

Wikipedia also has a useful article on Depression – differential diagnoses

[http://en.wikipedia.org/wiki/Depression_\(differential_diagnoses\)](http://en.wikipedia.org/wiki/Depression_(differential_diagnoses))

If you have access to UpToDate, you will find information on this topic for both patients and professionals.

Fatigue: many IC/BPS patients have a problem with fatigue. It may be tiredness resulting from lack of sleep due to nightly excursions to the bathroom and to the inability to relax due to constant pain. However, intense fatigue with memory and concentration problems, known by patients as ‘brain fog’, or extreme fatigue after very little physical exertion may indicate an autoimmune disease. If this seems to be a possibility, it may be worthwhile investigating whether there is an autoimmune disease present in addition to the IC/BPS. Fatigue on waking in the morning that improves as the day goes on may be an indication of depression. To be absolutely correct, the term Chronic Fatigue Syndrome (sometimes also called myalgic encephalomyelitis or ME) should only be used when no known disease has been identified that could be causing the chronic fatigue. However, in practice the terms chronic fatigue and chronic fatigue syndrome are often used synonymously. See also Chapter 7: Fatigue in IC/BPS patients.

Fibromyalgia syndrome (FMS) is a chronic, debilitating multisystem pain syndrome of unknown cause with widespread musculoskeletal pain and tenderness. The term fibromyalgia means pain in the soft fibrous tissues of the body: muscles, ligaments and tendons and in multiple tender points, but inflammation is not believed to be a characteristic of FMS. Current theory concerning the cause focuses on the theory of central sensitization. Fibromyalgia may be accompanied by a range of symptoms including morning stiffness, extreme fatigue, sleep disturbances, drug intolerance, irritable bowel syndrome, facial pain or pain around the temporomandibular joint (TMJ), pelvic pain and bladder disorders. Patients with FMS are also prone to tingling, numbness, dizziness and cognitive or memory disorders. FMS can vary in severity from person to person: some patients may have a mild form of discomfort, while others may suffer from a very severe and disabling form of FMS with extreme fatigue and pain. Some researchers have suggested that the term FMS may in fact include several sub-groups or phenotypes. Like IC/BPS, the course of this condition can be variable with exacerbations and remissions. For further information:

<http://www.fmaware.org/>,

<http://www.ukfibromyalgia.com/>

Rheumatoid arthritis (RA) is a chronic systemic, autoimmune connective tissue disease that mainly affects the synovial membranes of joints and is characterised by pain, swelling and stiffness of joints, usually symmetrically. As the disease progresses, the ligaments are damaged, there is erosion of the bone, resulting in deformity of the joints. This deformity of the joints is an important difference with other rheumatic diseases such as Sjögren's syndrome.

Gastro-intestinal disorders are frequently seen in association with IC.

- **Irritable bowel syndrome (IBS)**, a functional bowel disorder, is the most common disorder in IC/BPS patients, with symptoms including abdominal pain or cramp, alternating diarrhoea and constipation and a bloated feeling due to gas formation.
- **Inflammatory bowel disease (IBD)**, a group of disorders comprising Crohn's disease and ulcerative colitis, with weight loss, blood in the stools and diarrhoea at night, is also found more commonly in IC/BPS patients than in the general population. Commonly suspected to be of autoimmune origin.

For further information about the digestive system and how it works, go to:

<https://www.niddk.nih.gov/health-information/digestive-diseases>

Gastro-esophageal disorders (Gastroesophageal Reflux Disease or GERD) have also recently been linked with IC/BPS patients.

The National Digestive Diseases Information Clearinghouse (NDDIC) has useful information on IBS at:

<https://www.niddk.nih.gov/health-information/digestive-diseases/irritable-bowel-syndrome>

on IBD at:

<https://www.niddk.nih.gov/health-information/digestive-diseases/ulcerative-colitis>

on GERD at:

<https://www.niddk.nih.gov/health-information/digestive-diseases/acid-reflux-ger-gerd-adults>

Sensitive skin: Many IC/BPS patients have a problem with dry, itchy, sensitive skin. It is advisable to keep the skin well moisturized with cream or lotion for sensitive skin to reduce the dryness and this may also reduce some of the itchiness. IC/BPS patients should keep away from chemicals such as household cleaning products (wear protective gloves) and perfume, avoid using (perfumed) soap or any other products around the vulvar/genital area, take care with contraceptive devices containing chemicals such as condoms and spermicidal creams. If possible, they should wash their clothes with products specially made for sensitive skin that do not contain perfume, wear cotton underwear and loose clothes, avoid touching garden plants that may cause skin reactions and take care in the sun if they find that their skin is sensitive to sunshine.

Sjögren's syndrome is a chronic, autoimmune disease of unknown cause in which lachrymal (tear) and salivary glands malfunction. Its hallmark symptoms are sore, irritated eyes and dry mouth with a need to drink when eating because dry food otherwise sticks to the mouth and cannot be chewed or swallowed properly (so-called "cracker sign"). It is a systemic or "generalised" disease and may therefore affect many organs and systems of the body. Nine out of ten patients are women. Although it can affect any age group, the average age of onset is the late 40s. This disease is traditionally classified into two types: primary Sjögren's syndrome where the disease occurs alone and secondary Sjögren's syndrome when it occurs in association with another disease such as SLE, systemic sclerosis, rheumatoid arthritis and polymyositis /dermatomyositis. While some patients may experience only mild symptoms, in others their quality of life is seriously impaired by debilitating symptoms and extreme fatigue. It can often take many years for a patient to get a diagnosis, particularly in patients where the typical combination of irritated eyes and dry mouth is not recognized in patients in whom no autoantibodies can be seen and ESR is normal. In recent years, clinical studies, observation and surveys have led to an increased awareness that IC/BPS and Sjögren's syndrome can occur in association with each other and that Sjögren's syndrome may be

being underdiagnosed in IC/BPS patients. Some Sjögren's patients may have an autoimmune kidney condition of the distal tubules: distal Renal Tubular Acidosis (dRTA) which is a type of interstitial nephritis and causes a urinary acidification disorder (with increased urinary pH) while the blood becomes more acid with loss of potassium (hypokalaemia). This potassium ends up in the urine and can cause flares of burning bladder pain in an IC/BPS patient.

The term **Sicca Syndrome** or Sicca Complex is often used for dryness of the exocrine glands, particularly the eyes and mouth when there is no evidence of autoimmune disease present. While sicca symptoms occur in the vast majority of Sjögren's patients, not everyone with these symptoms has Sjögren's syndrome.

Further information on Sjögren's syndrome:

http://www.painful-bladder.org/pbs_ic_ass_dis.html

<https://www.sjogrens.org/home>

Information on dRTA: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4107275/>

Systemic Lupus Erythematosus (SLE) is a chronic, inflammatory, autoimmune connective tissue disease, involving many organs, with unpredictable flares and remissions. It may involve joints, skin, kidneys, lungs, heart, vascular system, gastrointestinal tract, central or peripheral nervous system and the bladder. A painful bladder disorder in SLE patients was known in the past as 'Lupus Cystitis' but is now generally referred to as IC/BPS. The symptoms and severity of SLE can greatly vary from patient to patient and may also undergo change in an individual patient over time. As in the case of IC/BPS, there is a high predominance of women patients. See:

<https://ghr.nlm.nih.gov/condition/systemic-lupus-erythematosus>

Thyroid disorders: The thyroid gland is situated at the front of the neck below the skin and muscle layers. It has the form of a butterfly with the two wings represented by the right and left lobes that wrap around the trachea. The function of the thyroid gland is to make thyroid hormone which regulates the body's metabolism and is essential for mental and physical development. The thyroid gland is prone to two extremes of disorders:

- Hyperthyroidism (it makes too much hormone)
- Hypothyroidism (it makes too little hormone).

Chronic thyroiditis is an inflammatory condition of the thyroid caused by an autoimmune disorder in which lymphocytes invade the tissues of the gland. The most common type of thyroiditis is Hashimoto's thyroiditis. It includes swelling of the thyroid gland and partial or complete failure to secrete thyroid hormones. Women are affected more than men.

Vulvodynia (or vulvar pain) is a distressing, painful condition, difficult to diagnose and difficult to treat. It is a broad collective term used to describe any chronic pain condition of the vulvar area (more than three to six months) and embraces a number of different types of vulvar disorder causing chronic or intermittent pain, burning, rawness and pain with intercourse. There are two main types of vulvar pain who may sometimes occur together:

- **Provoked Vestibulodynia (PVD) (also known as vulvar vestibulitis)** is pain or burning sensation caused by something touching the vestibule (entrance to the vagina). Pain is caused by sexual intercourse, insertion of tampons, riding a bicycle, gynaecological examination, tight clothes or any situation where the vestibule is touched. There is usually no pain if the area is not touched. Vestibulodynia is diagnosed by touching the vestibule with a Q-tip. Even light pressure such as this can cause pain.
- **Generalized Unprovoked Vulvodynia (GV) (previously known as dysesthetic or essential vulvodynia)** is spontaneous pain, burning, stinging or rawness on or around the vulva, labia, vestibule, clitoris or perineum most of the time, whatever they are doing. It is not dependent

upon touch or pressure but this can nevertheless exacerbate the symptoms. Urination may cause pain and burning. Generalized unprovoked vulvodynia is diagnosed when there is a history of relatively constant pain – although there may be periods of symptom relief - with no visible cause or other identifiable disorder such as infection.

For further information on vulvodynia, see: www.nva.org (National Vulvodynia Association, USA)

For further detailed information on IC/BPS and associated disorders, visit the IPBF website:

http://www.painful-bladder.org/pbs_ic_ass_dis.html :

“Interstitial cystitis and associated disorders” by Joop P. van de Merwe MD

“Interstitial cystitis and gastrointestinal disorders” by Joop P. van de Merwe MD as well as detailed information on Sjögren’s syndrome by the same author in both English and Dutch languages.

Table 3. Questions to assess the possibility of an IC/BPS patient having associated disorders as a useful first screening for the presence of these diseases

1. Allergy

- 1.1 Have you ever had shortness of breath, shock, angioedema, pruritis or urticaria after exposure to or ingestion of a particular drug, food, pollen, or contact with an animal?

2. Asthma

- 2.1 Do you have recurrent episodes of dyspnoea, coughing and wheezing?
2.2 Are these symptoms seasonal, or do they occur shortly after exposure to antigens such as animal dander, feathers, dust mites or mould?

3. Crohn's disease and ulcerative colitis

- 3.1 Do you often have abdominal cramp, particularly after meals?
3.2 Have you lost weight? (what was your normal weight and what did you weigh at that time?)
3.3 Do you often have diarrhoea or loose stools?
3.4 Do you often see red blood with stools?
3.5 Have you in the past had unexplained anaemia?
3.6 Do you have/have you had fistulas?

4. Fibromyalgia

- 4.1 Do you have diffuse musculoskeletal achiness, stiffness or exaggerated tenderness?
4.2 Do you have visible swelling of the joints? (suggests another disease)
4.3 Do you have paraesthesia, non-restorative sleep and are you easily fatigued?

5. Irritable bowel syndrome

- 5.1 Do you often have abdominal pain or discomfort in association with defecation?
5.2 Do you have abdominal pain in association with a change in bowel habit?
5.3 Do you have disordered defecation such as abnormal stool frequency, abnormal stool form, defecation straining or urgency, a feeling of incomplete bowel emptying, mucus with stools or a bloated or swollen abdomen?

6. Rheumatoid arthritis

- 6.1 Do you have chronic symmetrical swelling and pain in multiple joints?
6.2 Do you have generalized morning stiffness lasting more than 1 hour?

7. Sjögren's syndrome

- 7.1 Have you had daily, persistent, troublesome dry or irritated eyes for more than 3 months?
7.2 Do you have a recurrent sensation of sand or gravel in the eyes?
7.3 Do you use tear substitutes more than 3 times a day?
7.4 Have you had a daily feeling of dry mouth for more than 3 months?
7.5 Have you had recurrently or persistently swollen salivary glands as an adult?
7.6 Do you frequently drink liquids to aid in swallowing dry food?

8. Systemic lupus erythematosus

- 8.1 Does the sun cause redness on areas of your skin exposed to a normal amount of sunlight?
8.2 Do you often have mouth ulcers or sores?
8.3 Do you often have painful swelling of the joints in your hands and/or feet?
8.4 Have you ever had pericarditis, pleurisy or nephritis?

(Source: Joop P. van de Merwe MD, PhD)

CHAPTER 7 - FATIGUE IN IC/BPS PATIENTS: IMPACT & COPING

Fatigue is a potentially disabling condition that can cause mental and physical dysfunction, with a severe impact on the patient's relationships, home-life, employment and social life. It can cause physical incapacity, brain fog, inability to communicate to people around you, and an overwhelming sense of isolation.

Many IC/BPS patients suffer from fatigue, listlessness and lack of energy or drive. While fatigue is still frequently ignored, misunderstood, dismissed as psychosomatic or simply considered unimportant by many of the medical profession, it is also equally misunderstood by the patient's family and friends. This can create a very unsympathetic environment for a patient suffering from fatigue and make it so much more difficult to cope with the condition.

As with everything in IC/BPS patients, there are huge variations in fatigue varying from mild and fluctuating at one end of the scale and very severe at the other end, with an impact that may virtually paralyse the patient's life. Fatigue may on the one hand be temporary, the cause easily diagnosable and treatable, or it may be persistent, unexplainable and fail to respond to any treatment. A patient may have only physical fatigue, or a combination of physical and mental fatigue (known as brain fog).

One of the aspects that make fatigue so complex is that persistent tiredness or chronic fatigue can have multiple causes and any individual patient may be suffering from more than one cause of fatigue at the same time and therefore all of these will need to be addressed. And it is certainly not always easy to see what the cause or different causes may be, especially as the symptoms from different types of fatigue may be similar and overlap.

Causes of fatigue (see also Table 4)

Causes of fatigue can be roughly grouped under the following main headings:

- Sleep disruption
- Medication
- Physical (organ-based) diseases
- Psychological disorders
- Diseases without proven psychological or physical cause
- General

Sleep disruption

Lack of proper sleep is the first aspect that anyone is going to think of in relation to an IC/BPS patient. We know that IC/BPS patients vary greatly in their symptom levels, including night-time voiding, and this can even fluctuate in an individual patient depending on whether the patient is in a flare or in remission. But even only 2 or 3 times a night on a regular basis can cause considerable tiredness because some people find it very difficult to get off to sleep again once they've got out of bed. The most severe IC/BPS patients, or patients in a flare, may be out of bed every 20 minutes or worse, even sitting all night on the toilet, or wrapped up in a blanket on the bathroom floor.

However, we should not forget that many other aspects can contribute either to being unable to get off to sleep or to frequent waking in the night, leading to extreme tiredness:

- pain, not only in the bladder but also elsewhere; many IC/BPS patients may have one or multiple other pain syndromes which may cause pain at night.
- Restless legs syndrome, itching, burning, tingling: all of these can prevent you from sleeping.
- Medications: all kinds of medication can cause insomnia.

- Patients may be woken up by noise: from a snoring partner, crying babies, noisy traffic etc.
- Too much light inside or outside the home, from streetlights or outside security lights.
- Anxiety, work stress, and the stress, worry and sometimes panic of coping with IC/BPS can all prevent sleep.
- Many diseases and disorders can cause sleeping disorders or insomnia, e.g. fibromyalgia.

Therefore, each patient should carefully think about whether it is purely the bladder pain and need to void that is waking them (or keeping them awake), or whether something else has disturbed their sleep and they then feel their bladder discomfort and get out of bed. It may be purely the IC/BPS bladder in some patients, but in others perhaps a combination.

Physical and psychological impact of lack of sleep

“Frequent nocturnal awakenings, particularly during the first part of the night, decrease the restorative function of sleep and can cause daytime sleepiness and impaired cognitive function.”
(Chapple C. Introduction and conclusions. *European Urology Supplements* 6 (2007) 573–575)

According to the experts, proper, restorative sleep occurs in the first part of the night and it is likely to be this early part of the night that is most disturbed in IC/BPS patients. Adequate sleep is a basic requirement for good health. You need sleep for recuperation and restoration of physical and mental functioning. Without this proper sleep, a person deteriorates both physically and psychologically. The physical and psychological impact of sleep disruption is quite extensive and can have serious consequences as you can see from the list below:

- Fatigue and lack of energy
- Mood swings, irritability, tearfulness
- Lack of motivation
- Decreased concentration
- Memory lapses
- Motor performance impairment
- Disorientation
- Depression

(adapted from Marschall-Kehrel D. Update on nocturia: the best of rest is sleep. Urology. 2004 Dec;64(6 Suppl1):21-4)

Treating lack of sleep – useful tips for the IC/BPS patient

- It goes without saying that suitable treatment for the bladder pain and the frequency and any other pain should have absolute priority.
- If the distance to the bathroom is too far, it’s also a good idea for an IC/BPS patient to have a commode or an old-fashioned chamber pot or a portable camping toilet in the bedroom. The further you have to walk to reach the bathroom, the more time your body has to completely wake up, and the less likely you are to get off to sleep again when you’re back in bed. A toilet facility close by can reduce the risk of falls in the night.
- Cut down night-time voiding as far as possible or advisable by limiting drinking in the evening and avoid consuming any food or drink that you know will irritate the bladder or food and drink that is likely to keep you awake. But make up for this by drinking plenty earlier in the day to avoid concentration of urine.
- If you have to take medication that causes irritation in the bladder, either take it early in the morning or very late at night just before sleeping. But preferably change your medication to something that does not irritate the bladder.
- If you are being kept awake or woken up by noise of any kind, try using ear-plugs.

- If you can't do anything about disturbing light, wear an eye-mask.
- If lack of sleep is partly caused by anxiety or stress, counselling may be needed. IC/BPS patients can become very anxious and panicky about their bladder disorder and its impact on their life and of course the fact that treatment may not be working. They worry continually about what the future may bring. And some counselling could help here.

Medication causing daytime drowsiness

While some medication can cause insomnia, other drugs can cause drowsiness all day long. Unfortunately, so many treatments used for pain in IC/BPS have a sedative effect and make a patient feel like a zombie. However, many other drugs can have a sedative effect in some patients. Medicine intolerance experienced to varying degrees by some IC/BPS patients can make them react much more strongly to even the lowest dosages. It is therefore important to be aware that any medication could potentially either cause insomnia or daytime drowsiness or exacerbate existing chronic fatigue.

Physical (organ-based) diseases

Diseases causing tiredness include anaemia, hypothyroidism, heart failure, low blood pressure, infectious diseases including glandular fever. These can all be checked out by the doctor. Cancers also cause extreme fatigue. Any diseases causing chronic pain day in day out are very exhausting. Coping with a bladder disorder like IC/BPS is also very tiring because a patient can never really relax. They always feel that pain or irritation in the bladder and are exhausted by continually going to and from the bathroom.

Chronic fatigue

A special role is played here by systemic autoimmune diseases such as systemic lupus erythematosus and Sjögren's syndrome in which true **chronic fatigue** can be a totally disabling symptom. Chronic fatigue can also occur in fibromyalgia. When no identifiable disease or cause of the fatigue can be found, it is known as chronic fatigue syndrome.

Chronic fatigue is different to other forms of tiredness. A difference with the tiredness caused by lack of sleep is that autoimmune tiredness has no bearing on whether you have slept well or not. Chronic fatigue may fluctuate from week to week, month to month and year to year and it may wax and wane during the day with flares at specific times when you then feel flu-like, shivering, with a headache, total exhaustion and inability to think. You no longer have the energy to take any kind of action, to talk to people, pick up the phone or take a decision. With chronic fatigue, you lose your drive, your motivation, you may have memory lapses, no concentration and experience confusion. Physically, you feel unwell all the time. Your body feels uncomfortable, it aches and you can't tolerate tight clothes. You become exhausted after the slightest exertion. While rest may sometimes alleviate the fatigue for a short time, as soon as you are busy again the fatigue returns.

Advice to patients with chronic fatigue

Work out how to plan your routine each day depending on how you feel. If necessary, restructure your life, change your lifestyle. Do not take on more commitments than you can cope with. Learn to say no. Recognize when you are overdoing it before you collapse. Don't feel guilty about taking naps or siestas during the day. Discover how much exercise you need and can cope with. Take sufficient exercise, but don't overdo it. With chronic fatigue, you have to learn how to pace yourself, learn how to manage physical and emotional stress. Avoid overdoing things at times when you feel a bit more energetic since this can cause rapid burnout. At those rare moments when you have a window of energy, it is so tempting to try to catch up with all those tasks that have been neglected and piled up. It is important at all times to build in periods of rest and relaxation.

All patients should bear in mind that fatigue or daytime drowsiness can make driving or use of machinery dangerous.

Psychological disorders

While depression can cause fatigue, chronic fatigue can itself cause depression. Since the very nature of IC/BPS symptoms can make patients depressed, it becomes a vicious circle from which it is difficult to escape.

Impact on the whole family

Fatigue impacts not only the patient but the whole family and can cause disruption of the life of everyone in the family, including children. It can make the patient unable to run the household, keep to any routine, create a normal environment for the family, lead a normal social life or have a normal relationship. The financial impact of chronic fatigue is a very important aspect for the patient since people with chronic fatigue may not be able to hold down a job.

For further information, including treatment, see:

Sjögren's syndrome. Information for patients and professionals by Dr Joop P. van de Merwe.
Chapter 5 Treatment including a section on fatigue: www.painful-bladder.org/pdf/ch5.pdf,
Chapter 6 Fatigue: <http://www.painful-bladder.org/pdf/ch6.pdf>

Table 4: SOME CAUSES OF FATIGUE

A. Sleep disruption

- night-time frequency
 - . e.g. IC/BPS, OAB, CP, pelvic organ prolapse, polyuria
 - . timing of drinking (too much, too late)
- pain, itching, burning, restless legs
- medication -> insomnia or nightmares
- environmental disturbance
 - . noise
 - . light
 - . uncomfortable bed, too hot, too cold
 - . snoring, restless partner
- stress, anxiety, panic attacks

B. Medication causing fatigue, sleepiness, lethargy

e.g. opioids, anticonvulsants, antihistamines, anticholinergics, antidepressants, proton pump inhibitors, cough & cold remedies, chemotherapy, blood pressure medications, heart medications

C. Physical (organ-based) diseases

Anaemia
 Hypothyroidism
 Heart failure
 Low blood pressure
 Infectious diseases
 Systemic autoimmune diseases
 Cancer

D. Psychological disorders

Depression
 Burnout

E. Diseases without proven physical and psychological cause

Chronic fatigue syndrome
 Fibromyalgia

F. General

Excessive activity, over-exercising

References and Further Reading

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-Translational Andrology & Urology, Focused Supplement on interstitial cystitis/bladder pain syndrome
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