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Role of Central Sensitivity Syndromes in women with pelvic organ prolapse

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Role of Central Sensitivity Syndromes in Women with Pelvic Organ Prolapse

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Author's Declaration

At no time during the registration for the degree of Doctor of Medicine has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee.

Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment. This research has been conducted under a formal agreement with Plymouth University. This study was financed with the aid of a studentship from the R&D department of Derriford Hospital, Plymouth and carried out in collaboration with Southmead Hospital, Bristol, Royal Cornwall Hospital, Truro and Singleton Hospital, Swansea.

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“Incredible things can be done simply if we are committed to making them happen”

Sadhguru-2018

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Dedicated to my parents

Mrs Pushpa Vij and Mr Sudarshan Kumar Vij

ABSTRACT

Title- Role of Central Sensitivity Syndromes in Women with Pelvic Organ Prolapse.

Author- Monika Vij

Pelvic Organ Prolapse (POP) is a dysfunction of pelvic floor support and have an adverse effect on the quality of life (QOL). The predominant symptom is the feeling of a vaginal bulge. However, a considerable proportion of women report a sensation of dragging, or pelvic pressure vaginally without a bulge or large objective prolapse being present. A mechanism suggested to explain this anomaly describes the augmentation of pain transmission secondary to central sensitization (CS). This explanation is like the pathophysiological changes postulated for central sensitivity syndromes (CSS) (a term collectively used for a group of pain disorders like fibromyalgia, chronic fatigue syndrome, temporomandibular disorder, chronic pelvic pain, and interstitial cystitis). The purpose of this thesis is to determine whether patients with central sensitivity syndromes have different outcomes from the surgical treatment of prolapse, compared to those without CSS.

The survey explored the level of awareness about CSS amongst healthcare professionals managing pelvic organ prolapse and identified that there is gap in knowledge about CSS in this specific group. The second part explored the proportion of women with central sensitivity syndrome attending the gynaecology outpatient clinic and revealed that around 32% of women with pelvic organ prolapse, and 40% with other gynaecological problems had evidence of CSS. The third part of the thesis reviewed the literature around the impact of CSS on post-surgical outcomes. This demonstrated that there is limited evidence currently available on the role of CSS on surgical outcomes. The fourth part of the thesis compared the outcomes of pelvic organ prolapse surgery between the two groups (i.e. those with and without CSS) and found that women with

CSS had a lower level of satisfaction and impression of improvement with persistence of symptoms compared to women without CSS. The qualitative study explored women's views on reasons for poor outcome from surgery amongst women with CSS. Poor surgical technique and /or underlying unidentified bowel or bladder pathology was the perceived reason for poor outcome, rather than CSS.

The above findings suggest that there is suboptimal awareness about this condition, amongst healthcare professionals and patients. The findings of the study also suggest that the presence of underlying CSSs could be one of the contributing factors responsible for poor outcomes. These findings will enable clinicians to adequately counsel women with CSS for the possible outcomes of the surgery, while also enabling those patients to have more realistic expectations from the surgery.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

CS…….....Central Sensitisation

CSS…….....Central Sensitivity Syndrome

GOPD…….....Gynae Outpatient Department

FSS……...……...……Functional Somatic Syndrome

POP……...…….....…Pelvic Organ Prolapse

FM…….…….....…..... Fibromyalgia

CFS……...…….....Chronic Fatigue Syndrome

MUS……..…… Medically Unexplained Symptoms

TMJ……...……...… Temporomandibular Joint Disease

CSI…….....……Central Sensitisation Inventory

CPP……...…….....Chronic Pelvic Pain

IBS……...…….....…...Irritable Bowel Syndrome

POP-Q……..……Pelvic Organ Prolapse Quantification

PGII……..……...Patient Global Impression of Improvement

POP-SS..... …….....Prolapse Symptom Score

EGGS…….....……Expectation, Goals, Goal achieved, Satisfaction

Chapter 1 – Background and Review

1.1. Pain and Central Sensitisation

Pain is described by the International Association for the study of pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (Bonica JJ 1979; Loeser JD et al., 2008). It is usually regarded as a symptom of underlying pathology and encourages the individual to withdraw from harmful situations to protect the body while it heals and prevents impairment of its normal function (The Neurobiology of Pain,1983). Pain can be categorised as acute, often provoked by an injury or a specific disease, seen as serving a specific biological purpose; or as chronic, where it can outlast the normal time of healing, persisting for months or years.

Nociceptive pain perception usually begins with the stimulation of peripheral nociceptors, either somatic or visceral. Nociceptors are the specialised sensory receptors responsible for the detection of noxious (unpleasant) stimuli, transforming the stimuli into electrical signals. These are then relayed to the central nervous system, including the higher brain centres (Hazem AA et al., 2016).

Nociceptors typically have "unencapsulated" free nerve endings, which innervate the dermis (including connective tissue and arteriole walls) as well as extending into parts of the epidermis. Nociceptors are also found in viscera, joints and muscle tissue. The free nerve endings are polymodal since they can function as thermoreceptors, cutaneous mechanoreceptors, as well as nociceptors.

The sensory afferent fibres are divided into Aα, Aβ, Aδ and C fibres, which vary according to the degree of myelination and, hence, conduction speed; with Aα the fastest, and C fibres the slowest fibres. The primary afferent Aα fibres carry non-noxious stimuli from muscle spindles and golgi bodies. Aβ fibres respond to light touch and transmit

non-noxious stimuli. Aδ fibres respond to mechanical and thermal stimuli. These fibres are thinly myelinated and conduction speeds are much faster than the unmyelinated C fibres which also respond to chemical, mechanical and thermal stimuli.

Aδ and C fibres, which are distributed throughout the body (skin, viscera, muscles, joints, meninges) are historically thought to be the only primary afferent fibres carrying signals from somatic noxious triggers. However, it is accepted that there is some over-lap in function, such that Aδ and C fibres can carry non-noxious stimuli and Aβ fibres can carry noxious stimuli.

The threshold of nociceptors varies with their location. Cutaneous nociceptors and those supplying muscle typically have a high threshold of activation whereas visceral nociceptors have a lower threshold of activation (Miliner R et al., 2015). The somatic nociceptive neurons are differentiated to respond to high threshold input such as intense heat or sharp pressure. When stimuli reach this high threshold, first order nociceptive neurons transmit the signal to second order neurons in the dorsal horn of the spinal cord. Subsequently, the signals are transmitted to various regions of the thalamus and higher brain centres (Woolf CJ 2011).

The traditional understanding of pain considered the afferent system as only relaying the nociceptive signals rather than the system having the ability to modulate the signals. This scientific view was prevalent until 1960 (Woolf CJ 2011). However, the Spinal Gate theory proposed by Melzack and Wall (1965) first demonstrated that this relay system could be modulated by inhibition in the spinal cord (Melzack R et al., 1965). Further studies revealed that pain signalling is modulated by complex and interactive processes in both the peripheral and central nervous system (Willis WD 1985). Thus, the experience of pain can be both inhibited and stimulated. There continues to be an

incomplete understanding of nociceptor cell biology; however, the demonstration of the potential modulation of nociceptive signalling markedly helps improve our interpretation of this nociceptor influenced aspects of pain perception.

The state of persistent heightened responsiveness to a painful stimulus can be referred to as pain "sensitisation". Short term sensitisation following injury can be adaptive, for preventing the organism aggravating an injury, and hence, nurturing the healing process. However, in many clinical syndromes, pain can stop being a healthy protective mechanism for the organism and become a dysregulated process. Indeed, in some situations, chronic pain can become a disease process in its own right, as evidenced by the new changes incorporated in the latest version of the International Classification of Diseases (ICD), version 11(Khoury et al., 2017).

In these conditions, pain can arise spontaneously or can occur with innocuous stimuli (allodynia) due to a convergence of sensory processing. This convergence process is reflective of the development of central sensitisation and is believed to take place in the spinal cord and in pain networks directly controlled by the brain (Woolf CJ 2011). Pain can also present as an exaggerated and prolonged response to noxious stimuli (hyperalgesia) and can spread well beyond the site of injury (secondary hyperalgesia).

There are two types of sensitisation peripheral and central. In peripheral sensitisation, the nociceptor peripheral terminals can become ‘‘sensitised" after injury, reducing their threshold, particularly to heat stimuli within the site of injury where the terminal is exposed to inflammatory modulators as part of the "inflammatory soup" (Bishop T et al., 2010, Campbell JN et al., 1988).

In central sensitisation, there appears to be pain perception beyond the area of injury and the nociceptive activity also includes components of the system that do not normally respond, such as large low-threshold mechanoreceptor myelinated fibres.

Thus, central sensitisation results from changes in the properties of neurons in the central nervous system (CNS), and so can also produce pain hypersensitivity in non-inflamed tissue. It also increases pain sensitivity long after the initiating cause may have resolved and when no peripheral pathology might be present (Latremoliere A et al., 2009). Some of the potential mechanisms involved in central sensitisation are activation of NMDA receptor, altered gene expression in dorsal horn neurons, microglial activation (Wieseler-Frank J et al., 2005), decreased descending inhibition and thalamic and somatosensory cortex changes (Guilbaud G et al., 1992). These are considered further in the thesis.

1.2. Functional Somatic Syndromes or Medically unexplained symptoms (MUS)

Functional Somatic Syndrome (FSS) is defined as an illness without an organic disease explanation: devoid of any demonstrable structural lesion or biochemical change (Lipkin M 1969; Smith RC 1991). Historic expressions used are hysteria, imagined illness (hypochondriasis) or psychogenesis (Sharpe M et al., 1995). Newer descriptions applied for FSS are Medically Unexplained Symptoms (MUS) although this term appears to be becoming less accepted clinically and a further, more recently used term is Body distress syndrome (Budtz-Lilly A et al., 2015).

Conditions such as Irritable Bowel Syndrome (IBS), Chronic Fatigue Syndrome (CFS), Fibromyalgia (FM), Temporomandibular joint Disorder (TMJ), and Chronic Pelvic Pain (CPP) are some of the most common FSSs. They are typically described by the associated somatic symptoms whereas other clinical labels such as anxiety and depression highlight the psychological processes involved (Mayou R et al., 2002).

Around 1 in 6 primary care consultations involve Medically Unexplained Symptoms (Steinbrecher N et al., 2011). Barsky and Borus (1999) suggested that FSSs are

essentially expressions of somatization (Barsky AJ et al., 1999). It was also found that patients with FSS have high rates of psychiatric comorbidities especially anxiety and depression. However, it is difficult to say which is the cause and which is the consequence (Fiedler N et al., 1996) because most patients with FSS do not have a pathology or structural change in the areas where they report symptoms. For example, there are no definitive structural abnormalities or biomarkers for IBS, CFS or FM although they suffer from bowel symptoms, fatigue, and musculoskeletal pain respectively (Locke GR et al, 2004; Branco JC et al., 2010; Clauw DJ 2014; Morris G et al., 2013; Soares RL, 2014).

There is an on-going debate regarding the aetiology of FSS with some theories suggesting the possibility of anomalies in either the peripheral or central nervous system which cannot be easily assessed (Marianne R et al., 2017). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) introduced the term Somatic Symptom Disorder (SSD) to replace or augment prior diagnoses and no longer requires that symptoms have no medical basis to make the diagnosis. This may be appropriate in some situations.

1.3. Prevalence and Burden

It is hard to ascertain the extent of FSSs; however, studies show that the prevalence of Irritable Bowel Syndrome is 11% (Canavan C et al., 2014), Chronic Pelvic Pain (CPP) is between 5.7%-26.6% (Ahangari A 2014), Chronic Fatigue Syndrome is 9% (Skapinakis P et al., 2003) and Fibromyalgia varies between 0.2% and 6.6% (Marques AP et al., 2017) in community samples. There is also a significant overlapping of symptoms among these patients. Fibromyalgia and medically unexplained symptoms (MUS) result in significant psychosocial impairment, work disability, and increased health care utilization by patients (Kevin CF et al., 2015). For example, for patients with mild, moderate, and severe FM, annual direct health care resource costs in the USA were

estimated at $4,854, $5,662, and $9,318 per patient respectively. Annual mean indirect costs (including absenteeism, unemployment, early retirement, and disability) for subjects with mild, moderate, and severe fibromyalgia were estimated at $4,428, $14,664, and $29,996, respectively (Chandran A et al., 2012).

Other functional conditions are also associated with a substantial economic cost to the patient, healthcare, and society. For instance, extrapolated annual UK population costs for treating IBS is £45.6 -200 million (Wells NE et al., 1997; Akehurst RL et al., 2002). Similarly, the estimated annual direct costs of treating each case of CPP are approximately $7000(£5400) (Clemens JQ et al., 2009).

FSSs are strongly associated with reduced quality of life (QoL). Compared to healthy controls (HC), women with CFS report worse physical functioning, more bodily pain, loss of vitality, less productivity, worse general health, and social functioning, and, thus this condition has a significant impact on employment (Collin S et al., 2011; Anderson JS et al., 1997; Dickson A et al., 2009). Patients with IBS reveal the same pattern of QOL impairments (Monnikes H et al., 2011) as do patients with fibromyalgia (Hoffman D et al., 2008; Martinez JE et al., 1995). The studies also demonstrate that the functional limitations in FSS are as severe as those in medical disorders despite the absence of underlying organic pathology (Monica L et al., 2015). Thus, FSSs represent a significant burden to sufferers, their families, society and the healthcare systems they use.

1.4. Are FSSs discrete entities?

Studies suggest that FSSs are not entirely discrete syndromes. (Kanaan RA 2007). Wessely S et al (1999) found a considerable overlap of symptoms among FSSs such as - bloating or abdominal distension in 8 conditions, headache in 6, abdominal pain in 6 and fatigue in 6. Aaron LA et al (2000) demonstrated that while all patients with chronic fatigue syndrome (CFS) report fatigue, 86% of patients with fibromyalgia (FM) do too;

conversely, while the vast majority of FM patients report arthralgia, so do 88% of chronic fatigue (CFS) patients.

Aron and Buchwald reviewed 53 studies where patients with one FSS were assessed using the formal diagnostic criteria for another. They found that between 35 - 70% of patients with CFS met criteria for FM, 58-92% met criteria for IBS, and 53-67% showed multiple chemical sensitivities. Similarly, 75% of patients with FM met criteria for the temporomandibular disorder, 32-80% met criteria for IBS, and 55% described multiple chemical sensitivities (Aaron LA et al., 2000).

Similarly, other studies revealed that IBS is present in 39% of Chronic Pelvic Pain patients (Nickel JC et al., 2010). There is also a high risk of a patient developing a new FSS in the future if there is a presence of one FSS in an individual; Warren JW et al found that having any FSS was associated with 2.4 greater odds (95% CI, 1.3-4.7) of developing a new FSS in the following year (Warren JW et al., 2013).

It has been demonstrated that FSSs share many psychosocial and demographic correlates. Mood disorders especially depression and anxiety, are more common in patients with FSSs compared to patients with organic disease and healthy comparison groups (Henningsen P et al., 2003). They have also been thought to be linked with a history of abuse and maltreatment. Paras ML et al., 2009, revealed in a meta-analysis of 23 studies with 4640 subjects that lifetime history of sexual abuse was associated with significantly greater odds of developing functional gastrointestinal disorders (OR 2.43, 95% CI, 1.36-4.31) and CPP (OR 2.73, 95% CI 1.73-4.30).

A recent meta-analysis of 71 studies examining multiple forms of psychological trauma including emotional, physical, and sexual abuse confirmed that exposure to any trauma was associated with 2.7 greater odds (95% CI, 2.27-3.10) of meeting criteria for an FSS (Afari N et al., 2014).

As well as environmental factors, genetic factors might also have an impact on developing FSSs (Vehof J et al., 2014). MUSs and FSSs are also found to be more common in women than in men (Kroenke K et al., 1993).

Given the high rates of psychological comorbidity, it might be tempting to suggest that symptoms are largely due to catastrophizing, somatization or negative affect. However, mediation modelling approaches (a method to understand the relationship between dependent and independent variable through a mediator variable), demonstrate that psychological and environmental factors (e.g. neuroticism, abuse history, life events, anxiety, somatization and catastrophizing) account for just 36% of the variance in IBS severity and 42% of the variance in pain experienced by fibromyalgia patients (VanTilburg MAL et al., 2013).Given the above caveats, whatever the eventual full explanation, it seems unlikely that either specific physiological or psychological processes, alone, will account for the wide range of symptoms of FSSs.

1.5. FSS or Central sensitivity syndrome

Research has demonstrated that medically unexplained pain constitutes one of the important elements amongst all the symptoms of FSSs. For instance, IBS is characterized by pain in the lower or whole abdomen and pain associated with defaecation (Drossman DA et al., 2006).

Fibromyalgia (FM) is characterised by widespread pain including the back, neck, and extremities (Wolfe F et al 2010) and chronic fatigue syndrome (CFS) by headache, muscle pain, and joint pain without redness or swelling (Fukuda K et al., 1994); Temporomandibular disorder (TMD) is characterised by jaw pain, earache, headache, facial pain (Robert LG et al., 2015) and chronic pelvic pain (CPP) by pelvic pain and myofascial pain (Jane PD et al., 2010). Overall pain is also found to be the most common complaint for which patient with FSSs seek help (Hungin AP et al., 2005).

Recently, it has been proposed that these pain disorders are linked by a similar pathological process of dysregulated centrally mediated nociception, referred to as "central sensitization"(Lindsay LK et al., 2011).In addition to a common mechanism of pain, these disorders often co-occur (Aggarwal VR et al., 2006), may act as a catalyst for the development of one another (Diatchenko L et al., 2006) and the pain may also transition from localized pain to a widespread pain disorder (Holm LW et al., 2007).

Several of these disorders may have started from a peripherally mediated pain producing mechanism (inflammation and/or neural irritation). However, persistent nociceptive input can lead to physiological changes in the central nociceptive system, and, following the induction of central sensitization, painful sensations can arise independently of peripheral nociceptive input (Latremoliere A et al., 2009).

Given the potential shared pathophysiological mechanisms, these disorders, therefore, have been collectively termed by some researchers as "central sensitivity syndromes" (CSS) (Yunus MB 2008). This underlying connection might help us to understand the development of widespread hyperalgesia in some patients as well as provide a framework for why central sensitivity syndromes often overlap with one another. The resulting diagnosis of the disorder is largely dependent on the patient's main presenting complaint and the attending clinician's subspecialty (Aaron LA 2001).

Various combination of symptoms which might suggest the presence of CSS are:

- Widespread pain including abdominal pain, non-specific chest pain, atypical facial pain, burning mouth syndrome, chronic low backache, migraine, myofascial pain, chronic pelvic pain, joint pains.
- Chronic fatigue particularly post exertional malaise.
- Perceptual sensitivity to light, noise, aromas, and touch.

- Other symptoms including non-dermatomal paraesthesia, restless legs, temperature dysregulation, tinnitus, abdominal bloating, non- specific light headedness, poor concentration, and short-term memory.
- Other concomitant presentations including irritable bowel syndrome, anxiety, depression, symptoms of post-traumatic stress disorder.

The postulated aetiology is increasingly thought to be due to a process of central sensitization (Kevin CF et al., 2015).

A theoretical model which helps explain this and appears well accepted by patients is that of the Hyland Model (Michael EH et al., 2016). This proposes an intermediary theory, which incorporates both biological and psychological models to explain the evolution of central sensitivity syndromes. This has parallels with the bio-psycho-social model to help understand the pathophysiology and management of symptoms seen in CSS, but it is important to note that the biopsychosocial approach is also relevant in all chronic conditions and is not specific to CSS (Leah M et al., 2015).

The above literature provides a concise overview of the burden and impact caused by medically unexplained symptoms. It highlights the variability of terminology associated with Functional Somatic Syndromes and further supports the potential utility of an umbrella term such as Central Sensitivity Syndromes to describe a group of disorders which share common symptoms with no underlying pathology but with pain being the leading feature.

Whilst central sensitisation helps explain some dysregulated longer-term pain and hypersensitivity, the CS process does not invariably result in altered pain perception. An example of this is hyperacusis (where there is an increased sensitivity to certain levels of sound but does not necessarily result in pain). There is also debate as to whether the

cognitive symptoms noted in central sensitivity syndrome can be adequately explained by the central sensitisation model (Vardeh D et al., 2016).

As CS is considered to be the common phenomenon in CSSs it is important to understand the mechanism of central sensitisation and its assessment.

1.6. Mechanism of central sensitisation and its assessment

Central sensitisation is defined as a change in the functional state of neurons and nociceptive pathways caused by increased membrane excitability and synaptic efficiency or also by decreased inhibition on this system (Wolf CJ 1983).

Several possible phenomena involved include:

1) Activation of wide dynamic range neurons (WDR), which starts to respond to nociceptive and previously non- nociceptive stimuli (Hazem AA et al., 2016). These neurons carry the nociceptive stimuli to dorsal horn neurons in the spinal cord. Some of them are multi-modal responding to sensation from temperature, touch, pressure, and pain (Lindsay LK et al., 2011).
2) Progressive increase of responses provoked by a standard series of repeated stimuli (temporal windup which can be homosynaptic i.e. response due to activation of the same synapse or heterosynaptic i.e. activity in one set of synapses augments subsequent activity in other non- activated group of synapses) (Hazem AA et al., 2016).
3) Expansion of the spatial dimensions of the input; activating a series of changes that sustain longer than the initial stimulus (Latremoliere A et al., 2009).

As well as changes from activity dependent synaptic plasticity, changes in microglial and astrocyte function is also gaining popularity as a scientific explanation for the maintenance of central sensitisation (Chacur M et al., 2009; Gao YJ et al., 2009; Chiechio S et al., 2009). This will be described in the later part of the thesis.

One of the first studies on central sensitisation demonstrated secondary cutaneous hyperalgesia induced by intradermal capsaicin injection (via activation of the TRPV1 receptor). This study demonstrated three areas of hyperalgesia. The primary area close to the injection site lasting 1-2 hrs, then an intermediate area of dynamic tactile allodynia spreading beyond this central area of heat hyperalgesia lasting for several hours. The final area is the largest, extending further from the injection site and lasted for more than 24 hrs. The last component is defined as secondary sensitisation resulting from changes within the central nervous system (CNS) (LaMotte RH et al., 1991).

Further experiments indicated that capsaicin induced nociception is mostly transmitted via the C fibres and the transmission of information resulting in mechanical allodynia via low threshold myelinated fibres (Wolf CJ 2011). The stimulation of Aβ fibres evoking a non-painful tactile sensation before a capsaicin injection can subsequently result in the perception of pain if their receptive area is within the zone of mechanical hyperalgesia as demonstrated by Torebjork in 1992 (Torebjork HE et al., 1992). Similar findings were demonstrated by Koltzenburg et al using mustard oil as this could also activate TRPA1 receptors (Koltzenburg M et al., 1994). The central augmentation of Aδ fibres following a C- fibre stimulation can contribute to pinprick/punctate secondary hyperalgesia as demonstrated by Ziegler et al (1999) using intradermal capsaicin (Ziegler EA et al., 1999).

The noxious stimulation from capsaicin has produced central plasticity within the nociceptive system via activation of C-fibre nociceptors. As a result of this, the nociceptive system is responding to stimuli outside the area of injury and to low-threshold afferents that were not stimulated by noxious stimuli previously. It is thus hypothesised that there are activity dependent changes in the functional properties of neurons in the

dorsal horn of the spinal cord contributing to this pain hypersensitivity (Latremoliere A et al., 2009). Subsequently, similar changes were described in other studies particularly in laminae I and V of spinal dorsal horn neurons (Cook AJ et al.,1986); as well as in the spinal trigeminal nucleus (Burstein R et al., 1998); thalamus (Dostrovsky JO et al., 1990); amygdala (Neugebauer V et al., 2003) and the anterior cortex cingulate areas (Wei F et al., 2001).

The effects of central sensitisation can also be demonstrated using objective markers as well as from subjective pain measures. For example, the increased activity of neurons in the somatosensory cortex triggered by low threshold Aβ stimulation from within the capsaicin-induced zone of secondary hyperalgesia can be shown by functional MRI imaging (Baron R et al., 2000). Various alterations in the patterns of cerebral processing can also be identified by Magnetoencephalography (Maihofner C et al., 2010).

Early explanations of the molecular mechanism responsible for central sensitisation included the proposal that the induction and maintenance of acute activity-dependent central sensitization was dependent on NMDA receptors, (Woolf CJ et al.,1991) with key involvement of glutamate and its receptors. However, it is now perhaps better understood that central sensitization comprises two temporal phases- 1. The early phosphorylation-dependent and transcription-independent phase resulting mainly from rapid changes in glutamate receptor and ion channel properties (Woolf CJ et al., 2000). 2. The later, longer-lasting, transcription-dependent phase the synthesis of the new proteins responsible for the longer-lasting form of central sensitization (Woolf CJ et al., 2000).

While the ascending pain pathways play an important part in the development of chronic pain, there is growing evidence that descending modulation of pain also has a

significant role in the generation and maintenance of central sensitisation. The periaqueductal gray-rostral ventromedial medulla (RVM) system has been found to be a key component in the descending modulation of pain. Descending pathways can have a facilitatory as well as an inhibitory role (Suzuki R et al., 2004) and the predominance of descending facilitation is found to be a contributing factor to the development of central sensitisation and widespread hyperalgesia (Heinricher MM et al., 2009). In situations resulting in repeated nociceptive stimulation, changes in the neurons of the RVM may produce an imbalance in facilitatory influences, leading to the maintenance of hyperalgesia (Porreca F et al., 2002). Alterations in the ascending pathways in central sensitisation are likely to combine with abnormal descending modulation to initiate and maintain hypersensitivity and pain in Fibromyalgia (FM) (Staud R et al., 2006).

1.7. Receptors and Neurotransmitters responsible for central sensitisation

1. **Glutamate,** an excitatory neurotransmitter, binds to several postsynaptic receptors on the spinal dorsal horn, including the ionophores amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor (AMPAR), N-methyl D-aspartate (NMDAR), kainate (KA), metabotropic receptors (coupled to G protein) and other subtypes of glutamate receptors (mGluR).

   AMPAR and NMDAR are expressed in high densities in the superficial laminae of the dorsal horn. Activation of NMDAR is important in both initiating and maintaining activity-dependent potentiation as its blockade by non-competitive (MK801) or competitive (D-CPP) NMDAR antagonists prevent and reverse the hyperexcitability of nociceptive neurons induced by nociceptor conditioning inputs.

   In normal conditions, NMDAR ionophore is blocked by magnesium ion (Mg++). Sustained release by glutamate nociceptors, neuropeptides, substance P (SP) and gene related peptide calcitonin (CGPR) leads to enough depolarization of plasma

membrane, forcing MG++ ion to leave the NMDA receptor pore. This then allows glutamate by binding to the receptor to generate an internal current and Calcium ion inflow (Hazem AA et al., 2016).

A large amount of calcium ion inflow activates numerous intracellular pathways which can contribute to both development and the maintenance of central sensitization (Mayer ML et al., 1984; Wolf CJ et al., 1991). The activation of mGluRs by glutamate also seems to be important for the development of central sensitization.

2. **Substance P-** Another neurotransmitter playing a part in central sensitisation is Substance P, co-released with glutamate by unmyelinated nociceptors (C fibres) (Afrah AW et al., 2002; Khasabov SG et al., 2002). Substance P binds to the neurokinin receptor -1(NK1) resulting in long-lasting membrane depolarization.
3. **Calcitonin gene-related peptide (CGRP),** synthesised by small neurons participates in central sensitisation due to activation of protein kinase A and C by CGRP1 postsynaptic receptors. There is also an increase in brain derived neurotrophic factor (BDNF) release from trigeminal nociceptors by CGRP, which is a synaptic modulator and released in the spinal cord. (Sun RQ et al., 2003).
4. **Bradykinin** a pro-inflammatory substance activating and sensitizing the primary afferent is produced in the spinal cord in response to intense peripheral noxious stimuli and acts by means of its B2 receptor, which is expressed by dorsal horn neurons. This increases synaptic efficiency by activating protein kinase A (PKA), protein kinase C (PKC) and kinases regulated by extracellular stimuli (ERK). ERK may also be activated by the serotoninergic descending pathway (5-HT) involving receptor 5-HT3 and possibly receptor 5-HT7. (Woolf CJ 2011).
5. **Calcium-** Increased intracellular Calcium ions seem to be a primary trigger for the development of central sensitization. Increased intracellular calcium promotes

AMPAR and NMDAR receptors to be phosphorylated by PKA/PKC changing the activity of receptors. AMPAR and NMDAR receptor phosphorylation during central sensitization increases the density and activity of such receptors leading to post-synaptic hyperexcitability. This can trigger the activation of intracellular pathways which support central sensitisation and include phospholipase C pathway (PLC) and PKC, phosphatidylinositol-3-kinase pathway (PI3K) and protein kinase system pathways.

6. **Protein Kinase C (PKC)** activation decreases NMDAR Mg++ block and making it easier for the NMDAR activated state (Chen L et al., 1992). Activated PKC also decreases inhibitory transmission, reducing descending inhibition via the periaqueductal gray matter PAG (Lin Q et al.,1996). Disinhibition is another mechanism resulting in fibres becoming more susceptible to excitatory stimuli and will also help maintain the process of central sensitisation.

1.8. Summary of Mechanism of Central sensitisation

Figure 1 and Figure 2 summarise the possible mechanism of CS as well as the receptors involved

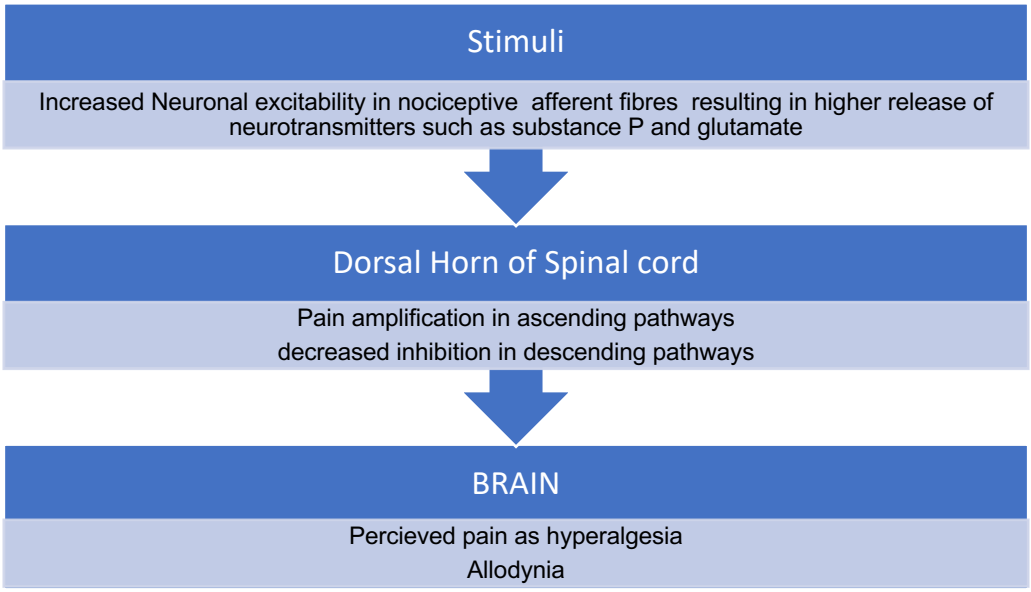

Figure 1: Showing abnormal pain signalling.

Mechanisms identified in common painful conditions within the umbrella of Central Sensitivity Syndrome (CSS)which support the phenomenon of Central Sensitisation:

1) Fibromyalgia (FM): The physiological and biochemical correlates of FM that supports the concept of central sensitisation are:

- Reduced pain thresholds
- Increased sensitivity outside of typical tender point locations
- Expansion of pain receptive area
- Increased level of Substance P and nerve growth factor in cerebral spinal fluid
- Abnormal wind up
- Persistent prolonged pain even after the removal of painful stimuli

(Dadabhoy D et al., 2008; Staud R et al., 2001).

The neuroplastic changes of central sensitisation have been demonstrated in FM patients with the help of functional magnetic resonance imaging (fMRI) (Gracely RH et al., 2002).

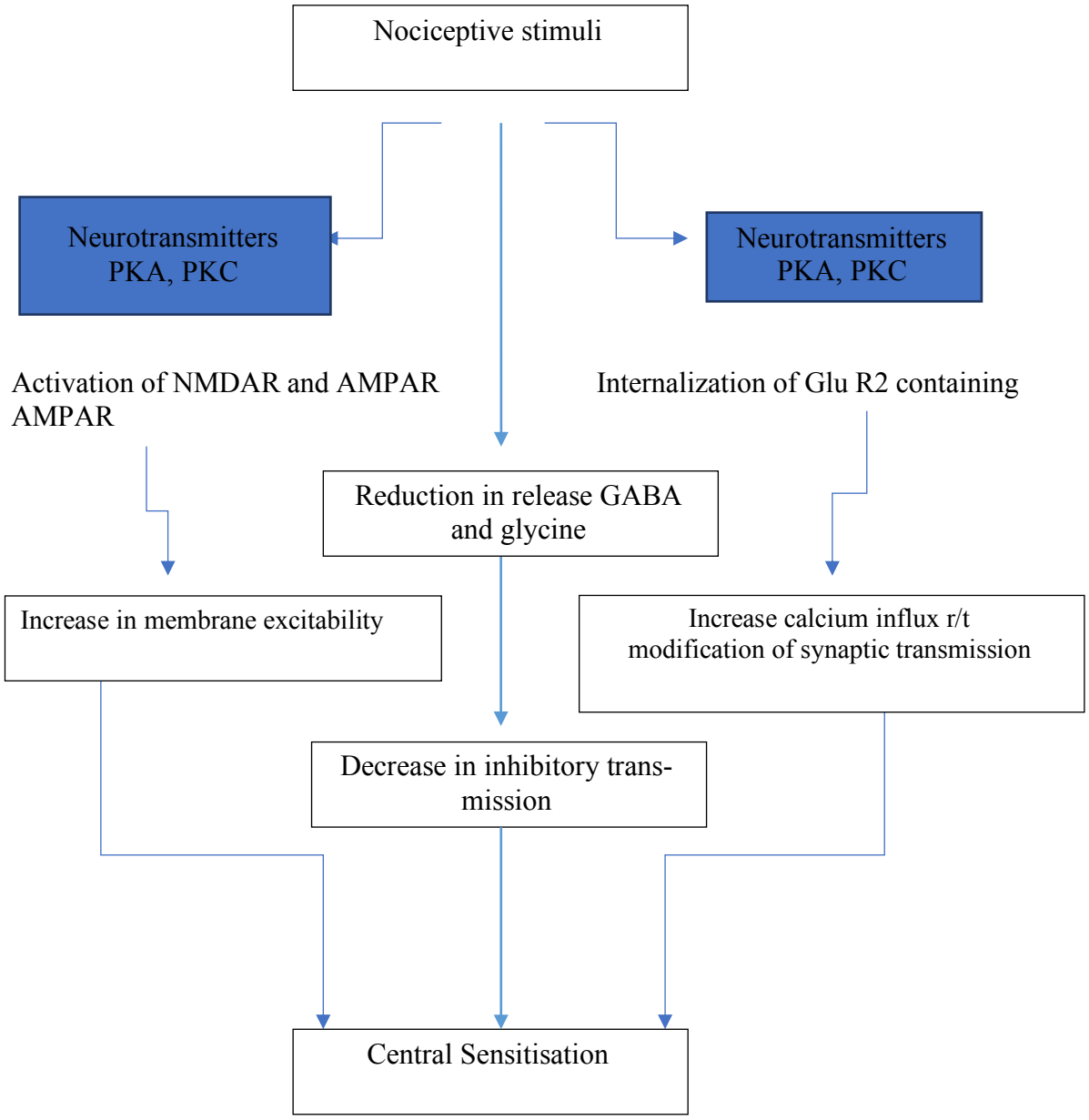

Figure 2: Neurotransmitters and receptors involved in possible mechanism of CS. (PKA/PKC-Protein Kinase A/C; Glu R1- Glutamate receptors, AMPARs- amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors).

2) Temporomandibular joint disorder (TMD):

- Alterations in the central nervous system pain regulatory system (Sarlani E et al., 2005).
- Increased sensitivity to experimental pain modalities both at temporomandibular region and at regions away from head and neck (Sarlani E et al., 2005).
- Reduced pressure pain thresholds both contralaterally and ipsilaterally.
- A Defective central inhibitory mechanism (Sarlani E et al., 2003).

3) Migraine:

- Increased excitability of medullary dorsal horn neurons which can be continued even after the removal of peripheral stimuli (de Tommaso et al., 2002).

4) Chronic low back pain and neck pain:

- Decreased pain thresholds, higher pain response, more widespread and longer duration of pain as demonstrated in various experimental pain studies (O'Neill S et al., 2007; Staud R et al., 2007).

In summary, there is strong evidence supporting the concept of central sensitisation to help explain the development of these painful disorders collectively labelled as Central Sensitivity Syndromes. However, further scientific enquiry is required to understand why some of these presents with focal pain symptoms rather than more widespread pain (for example, characteristic diagnostic features are seen in patients with interstitial cystitis on cystoscopy) while some of the patients develop centrally mediated pain disorders like FM.

1.9. Evidence of Neuroendocrine or autonomic abnormalities in CSSs

Neuroendocrine and autonomic nervous system dysfunction could contribute to many of the symptoms of CSSs. Previous studies have noted that there is either hypo or hyperactivity of both the hypothalamic pituitary adrenal axis (HPA) and sympathetic

nervous system in patients with FM and related painful conditions. However, an abnormal HPA as well as sympathetic dysfunction is not present in all but seen only in small group of patients with FM (Demitrack MA et al., 1998; Crofford LJ 1998) and data now suggests that these hormonal and autonomic changes are a possible consequence of pain or early life stressors rather than causing it (Mclean SA et al., 2005).

1.10. Evidence of immune dysfunction and abnormal cytokines in central sensitisation

Although the main body of expert opinion suggests that FM and other related CSSs are not autoimmune disorders, there is some evidence that immune system may have a role in their pathogenesis (Gur A et al., 2008). The most common finding is an elevation of IL-8, a cytokine associated with the sympathetic function (Bazzichi L et al., 2007). However, this area is still underexplored and needs further research.

1.11. Role of "small fibre neuropathy" in central sensitisation

Many studies have shown that there is decreased intra-epidermal nerve fibre density (i.e. small fibre neuropathy) in patients with FM (Caro XJ et al., 2015; Levine TD et al., 2015). The reduction in nerve fibre density is a very non- specific feature observed in over 50 different pain and non-pain conditions (Clauw DJ 2015). These findings were created in an animal model of central sensitisation by increasing the insular glutamate (Harte SE et al., 2017) and it has been suggested that this non-specific finding reflects adaptive structural and functional reorganisation of peripheral nervous system rather than due to changes in CNS (Harte SE et al., 2018). Overall, this area needs more investigation to confirm or refute any role of small fibre neuropathy in central sensitisation.

1.12. Role of gliopathy in central sensitisation

In addition to the above mechanisms, there is growing evidence that there is a potential role of glial cells in the initiation and maintenance of chronic pain. Three types of glial

cells which are said to be involved are microglia and astrocytes of CNS and satellite glial cells of dorsal root and trigeminal ganglia. (Ji RR et al., 2013). Some of the mechanisms involved are: upregulation of glial markers such as glial fibrillary acidic protein (GFAP) along with changes in glial network and synthesis and release of glial mediators like cytokines and chemokines. These glial mediators are found to be able to modulate excitatory and inhibitory transmission at pre, post, and extra synaptic sites. Detloff MR et al., described the contribution of dysfunctional glial mechanism in the development of central neuropathic pain after spinal cord injury (Detloff MR et al., 2008). Thus, chronic pain could be due to a "gliopathy," that is, dysregulation of glial functions in the central and peripheral nervous system. Further understanding of the role of glial cells in chronic pain and central sensitisation may help us to develop potential treatment strategies which target only the negative influence of glial cells and not the neurons.

1.13. Clinical assessment of Central sensitisation

Symptom characteristics of CS are observed across many different chronic pain conditions (Julien N et al., 2005; Campbell JN et al., 2006; Drewes AM et al., 2006; Woolf CJ 2011; Nijs J et al., 2014; Fingleton C et al., 2015). It is difficult to diagnose as there is no universally accepted definition or guideline criteria for diagnosing CS.

The Pain Sensitivity Questionnaire (PSQ) and the Central Sensitivity Index (CSI), are two instruments which have been developed and validated (Ruscheweyh R et al., 2009; Mayer TG et al 2012; Nijs J et al., 2014) to assess various clinically relevant pain ratings. Significant correlations have been observed between PSQ scores and pain intensity ratings (Ruscheweyh R et al., 2009; Sellers AB et al., 2013).

The CSI was originally designed to capture the patient's multiple somatic and emotional symptoms relating to central sensitization (Mayer TG et al., 2012). Part A of the

CSI assesses 25 symptoms common to central sensitivity syndromes (CSS) with a Likert scale from 0 (never) to 4 (always).

The total score ranges from 0 to 100, and higher scores indicate a greater degree of symptomology relating to CSS (Neblett R et al., 2013).

Part B of the CSI helps ascertains whether subjects have previously been diagnosed with one or more specific CSS diagnoses.

A CSI score>40 is deemed supportive of a diagnosis of CSS. The following severity ranges have been recommended:

- Subclinical = 0 to 29;
- Mild = 30 to 39;
- Moderate = 40 to 49;
- Severe = 50 to 59;
- Extreme = 60 to 100 (Neblett R et al., 2016).

Validation studies on the CSI have indicated a high sensitivity and specificity for the presence of an underlying CSS. The initial psychometric validity and clinical utility of the CSI were evaluated in two parts. In the first section, the CSI was evaluated for test-retest reliability and internal consistency. A factor analysis was then used to identify specific items.

In the second section, validation was undertaken by comparing scores between four subject groups, including fibromyalgia (FM), chronic widespread pain (CWP), regional chronic low back pain (CLBP), and a normative control group (Mayer TG et al., 2012).

A recent systematic review of the measurement properties of the CSI suggests that this assessment instrument yields reliable and valid data which can help quantify the overall severity of a CSS (Scerbo T et al., 2018).

The CSI is currently widely used as a useful tool to identify a CSS, however, its use as an alternative to measures relating to neuropathic pain is under debate. One clinical and experimental research method used for assessing pain sensitivity is by quantitative sensory testing (QST) (Roger AC et al., 2018) (See below pg. 31).

A few other questionnaires have been developed such as the pain DETECT questionnaire used for assessing neuropathic components in chronic musculoskeletal pain, e.g. Chronic low back pain (LBP) (Freynhagen R et al., 2006) and Osteoarthritis (OA) (Hochman JR et al., 2013). Recently, a mechanism-based classification was also developed by Smart (2012), which includes signs and symptoms suggestive of CS in patients with low back (leg) pain, but the authors did not adequately indicate how these criteria should be used in day to day clinical practice (Smart KM et al., 2012).

To improve the assessment of any developing pattern of pain sensitisation, it is useful to undertake a clinical mapping of the pain including the referred pain areas, as well as mapping areas with sensory hyposensitivity or hypersensitivity which can be followed quantitatively over time.

Receptive field expansion and perceptual changes into a more diffuse pattern of the pain can be observed in patients developing additional painful comorbidities for example in patients with knee OA, development of hand OA is a risk factor for the presence of diffuse generalised pain (Thompson LR et al., 2010).

1.14. Specific quantitative experimental tools for assessing CS

Clinical Quantitative Sensory Testing (QST) is one of the proposed methods to assess degree of central sensitisation. The defining feature of altered pain processing seen in central sensitisation was originally demonstrated in conditions such as FM by eliciting tenderness on palpation. Thereafter, QST was utilised to characterise pain and sensory mechanism in CS (Arendt-Nielsen L 2015; Wylde V et al., 2017). Various stimuli

(thermal, electrical, chemical) are used, utilising different techniques (e.g. electrophysiology or imaging). In this method, the stimulus (mechanical, thermal or electric) is undertaken systematically on the area under review. The responses to these stimuli which include nonverbal behaviour (e.g. withdrawal), unpleasantness, a rating of the perceived stimuli intensity is recorded to measure sensory gain or loss. The previous studies have demonstrated a bell-shaped distribution curve in pain sensitivity across general population and most patients with chronic pain conditions (as of CSS) were found to be to the right side of the distribution curve (Ablin K et al., 2009; Gwilym SE et al., 2009; Giesecke J et al., 2004).

Clinical mapping of pain areas is also useful to understand whether a given condition is localised to a certain neuronal segment or has spread across segments (Arendt-Nelson L et al., 2018)

The efficiency of endogenous pain modulation networks can be measured by QST. Further QST measures which can elicit altered endogenous pain modulation in patients with central sensitization include assessments of painful after-sensations (pain sensations that are slow to disappear after termination of the painful stimulation (Staud R et al 2007), and a counterbalance analgesia (an out of balance reduction in perceived pain after a slight decrease in the intensity of painful stimulation. (Hermans L et al., 2016).

Simple methods such as tapping the skin with a nylon filament can also be used as a bed side testing of cutaneous temporal summation (Nikolajsen L et al., 1996) but for more standardisation automated user-independent methods, for example, thermal (Kong JT et al., 2013), or pressure (Nie H et al., 2009) should be utilised. These tests are used to elicit temporal summation seen in CS (which refers to an increase in the perceived intensity of pain in response to repeated stimuli of equal physical strength).

Conditioned pain modulation (CPM) is believed to represent the human behavioural correlate of diffuse noxious inhibitory control (DNIC). DNIC alludes to the pain modulatory pathway, often described as 'pain inhibits pain' (Le Bars D et al., 1979). It happens when the response from a painful stimulus is inhibited by another noxious stimulus. CPM methods probe for the absence or impairment of inhibitory mechanisms. Although deficient CPM has been observed in a subset of healthy individuals (Potvin S et al., 2016; Schoen CJ et al., 2016), it is more common in individuals with FM and other chronic pain conditions (Granot M et al., 2008; Nir RR et al., 2015). Potvin S et al in 2016 proposed that the patients can be divided into two groups:

1. CPM reducers (resulting in pain inhibition)
2. CPM increasers (resulting in pain facilitation)

Another cohort study involving 2199 healthy volunteers demonstrates the distribution of CPM responses. This study hypothesises that those patients in the lower quartile could be more prone to develop chronic pain and those in the upper quartile who may, on the other hand, have a more protective CPM framework (Skovbjerg S et al., 2016). CPM viability decreases with age (Grashorn W et al., 2013) and is affected by gender (Martel MO et al., 2013) and psychosocial factors such as depression (Nahman-Averbuch H et al., 2016). This might explain why psychiatric and psychological disorders are sometimes associated with symptom correlates for central sensitisation (CS) in the absence of any specific peripheral nociceptive triggers.

A metanalysis undertaken in 2012 confirmed that CPM is debilitated in the majority of chronic pain conditions (Lewis GN et al., 2012) and clinically decreased CPM corresponds to increased postsurgical pain and analgesia requirements, with the successful response to centrally acting analgesics (Edwards RR et al., 2005; Yarnitsky D 2015).

In summary, despite the multiplicity of experimental and clinical evaluations that have been undertaken on central sensitisation, there is a continuing paucity of understanding regarding its pathophysiological basis. In addition, variation has been observed in the development of the degree of sensitisation across different chronic pain patients suggesting that central sensitisation may be a spectrum instead of being a dichotomous concept (i.e. present or absent).

The clinical manifestations of CSSs may vary in different individual in different pain conditions. Therefore, there is a growing need to develop specific assessments to analyse sensitisation in specific pain conditions. For instance, having specific tools to analyse the presentation of CS in musculoskeletal as opposed to visceral chronic pain conditions.

Moreover, the scientific endeavour of linking pain phenotype with the treatment outcome (surgical, conservative) in the context of pain is still at an early stage. It is also essential that tools are also developed which can improve the sensitivity and specificity of the predictors of the treatment outcome (Arendt-Nielsen L 2018).

1.15. Pelvic organ Prolapse and central sensitisation

Pelvic Organ Prolapse is a herniation of the pelvic organs (uterus, cervix, bladder, rectum) through the vagina due to loss of pelvic floor support (muscle and fascia) usually secondary to childbirth injury.

Pelvic organ prolapse (POP) is a frequent indication for hysterectomy and pelvic surgery in women, with an annual age-related (surgical) incidence in the range of 10 to 30 per 10,000 women confirmed in several large surgical database studies. For example, the National Health Service (England) Hospital Episode Statistics (HES), shows that the number of admissions for prolapse surgery was 1/1000 women in 2005 (Dhinagar

S et al., 2009). Out of 194,107 urogynaecology patients, 71,350 (36.6%) had prolapse surgery between 2008 and 2017 in England (HES data 2018).

Around one in 12 women reports symptoms of prolapse (Cooper J et al., 2015) with a lifetime risk of surgery of 12-19% (Olsen AL et al.,1997; Wu JM et al., 2014; Smith FJ et al., 2010). These numbers might increase with the increasing ageing population and rising obesity (De sam Lazaro S et al., 2016).

The population prevalence for POP beyond the hymen (>stage 2) is probably between 3 and 6%, however the loss of uterine support or vaginal support is seen in 30-76% women populations seeking gynaecological care. (Ellerkmann RM et al., 2001; Swift SE 2000; Trowbridge ER et al., 2008).

The prevalence of POP increases with age. There are suggestions that prevalence increases by 40% with each decade of life (Swift S et al., 2005).

The risk factors for pelvic organ prolapse are higher parity (Mant J et al., 1997), vaginal childbirth (Lukacz ES et al., 2006), and forceps delivery (Moali PA et al., 2003), advancing age (Swift S et al., 2005), obesity, chronic constipation, occupations involving heavy lifting, and connective tissue disorders such as those associated with variation of collagen type1 gene (COL1A1) (Cartwright R et al., 2015).

The principal symptom manifested in prolapse is the feeling of a bulge within the vagina that can be seen or felt (Barber MD et al., 2006). A significant proportion of women might also complain of a dragging sensation or pelvic pressure (Barber MD 2005). Other associated symptoms include urinary incontinence, overactive bladder, voiding difficulty, position change to start or complete voiding, incontinence of flatus or faeces (liquid or solid), a feeling of incomplete emptying, faecal urgency, dyspareunia, decreased sensation or pain in the vagina, bladder or rectum.

Women can present with single or combination of symptoms. Other than the vaginal bulge, none of the symptoms are specific for POP and considerable overlap exists with other pelvic floor disorders (Barber MD et al., 2006).

Pelvic examination is required to define the extent of POP/prolapse and also to identify the segments of the vagina affected. The pelvic organ prolapse quantification system (POPQ) is the grading system for prolapse with the highest reliability and is the most widely used system. This examination defines systematically the amount of anterior, posterior, and vault/apical segment prolapse in centimetres relative to a fixed anatomical structure—the vaginal hymen (Bump RC et al., 1996).

Additional testing is required only when associated bladder or bowel symptoms are present e.g. urodynamics, defecating proctography, anal manometry, and imaging.

The treatment options for the management of POP include both conservative and surgical management. The conservative management strategies are pelvic floor muscle training (PFMT) and insertion of a vaginal pessary along with lifestyle advice e.g. weight and avoiding constipation. Supervised pelvic floor muscle training is advised to be undertaken at least for 12-16 weeks (Hagen S et al., 2014; Wiegersma M et al., 2014). Hagen S et al showed improvement in prolapse symptoms in 45% of women whereas, Wiegersma M et al in her study demonstrated improvement in all prolapse symptoms in 57% of women with POP following 3 months of PFMT.

Vaginal Pessaries are the mechanical devices inserted in the vagina to reduce the prolapse. There are different type of pessaries (e.g. Gellhorn, ring, shelf). Cundiff GW et al (2007) conducted a randomised crossover trial to compare symptom relief of POP with ring pessary (with support) and Gellhorn pessary. They found that both types of pessaries are effective and equal in relieving symptoms of bulge, protrusion and voiding difficulties (Cundiff GW et al., 2007). However, overtime a majority of women opts to

discontinue the pessary. Sarma S et al in 2009 found that only 13.7% women continued using pessaries for the treatment of pelvic organ prolapse over a period of 6 years. About 27.5% discontinued due to complications experienced and 29.9% discontinued as they wanted the surgery. Various complications encountered were bleeding, extrusion, pain, vaginal discharge etc and the complication rate noted in this study was 56% (Sarma S et al., 2009).

The aim of the surgical treatment is not only to restore anatomy but also to improve bowel, bladder, and sexual function. Surgery is usually offered to women who have failed conservative treatment and/or with a stage 2 POP or beyond on examination and who report bothersome symptoms. The risks associated with surgery include haemorrhage, recurrence, trauma to bladder, bowel, internal organs, dyspareunia.

It is therefore important to assess the symptoms and their effect on quality of life in order to select the appropriate treatment and in some cases by preventing unnecessary surgery with its attendant risks.

For example, in the clinical setting, it has been observed that a significant proportion of women can present with heaviness or dragging sensation without a physically confirmed bulge/prolapse on examination. It is known that anomalies exist between the pathology i.e. prolapse and the degree of dragging sensation experienced by the patient. A mechanism suggested to explain this anomaly, describes the augmentation of pain transmission secondary to central sensitization (CS). Thus, the explanation is similar to the pathophysiological changes postulated for central sensitivity syndromes like Fibromyalgia and chronic fatigue syndrome.

Specific presentations such as hyperacusis (increased sensitivity to sounds, usually to specific frequencies and volumes) are significant but under recognised symptoms in conditions such as FM (Aries PS et al., 2017); Could a dragging sensation in the

absence of objective prolapse also be a poorly understood symptom of FM or other CSSs rather than due to prolapse? Current medical literature provides little clarification to this question.

Some evidence base relates to the potential role of Levator myalgia as a contributor to pelvic floor pain and sexual dysfunction. This has been reported in 24% of female patients attending a urogynaecologists practice (Adams K et al., 2013).

Levator myalgia might be considered as another manifestation of central sensitisation, with pain as well as pelvic pressure, vaginal bulge, and urinary and defecatory dysfunction (Adams K et al., 2014).

Previously studies have shown that female patients with fibromyalgia (FM) are more likely to have had a hysterectomy compared with those without FM and that their surgery does not relieve the symptom of pain (Pamuk ON et al., 2009; Santro MS et al., 2012).

Likewise, patients with Chronic Pelvic Pain (CPP) when contrasted with those without CPP appear to have worse outcomes or even worsening of the symptoms after revision following transvaginal mesh surgery for POP (Danford JM et al., 2015).

FSSs were found to be an independent risk factor for hysterectomy in patients with bladder pain syndrome (BPS)/interstitial cystitis (IC). A retrospective study by Warren et al demonstrated that 12% of women with BPS/IC underwent hysterectomy (Warren JW et al., 2014). The risk of hysterectomy was higher in the patients with BPS/IC than in non-BPS/IC cohort (Lee MH et al., 2016). It was suggested that women who have multiple FSSs and think that hysterectomy might relieve their pain should try alternative therapies including treatment of the FSSs rather than surgery (Warren JW et al., 2014).

Female patients with FM appear to report considerably more severe symptoms relating to pelvic floor complications compared to women without FM when attending urogynaecology practices although they had been in the similar age group (Jones K et al., 2015). It is considered possible that enhanced sensory and nociceptive processing may raise the level of awareness amongst female patients regarding the symptoms of organ prolapse in comparison with patients without FM. It has been suggested that this enhanced sensory processing could be due to the lack of activation of endogenous inhibitory systems (Julien N et al., 2005).

The available literature also provides little further clarification as to whether women with FM have different outcomes from the surgical treatment of pelvic organ prolapse than women without FM (Jones K et al., 2015). This information could have an important influence on decision making particularly as to whether to continue conservative treatment rather than offer surgical intervention.

1.16. Summary and Purpose of the study

The findings observed so far from this review can be summarised as follows:

FSSs or CSSs can be considered as important sources of increased clinical complexity for healthcare service providers. These conditions have a negative effect on QOL and affect patient care. Central sensitisation appears to be the common underlying potential mechanism.

POP is a dysfunction of pelvic floor support. This can have a detrimental effect on QOL and is seen in 30-70% of gynaecological consultations. The most predominant symptom of prolapse is the feeling of a vaginal bulge. However, a considerable proportion of women report a sensation of dragging or pelvic pressure vaginally without a bulge or large objective prolapse being present.

Levator myalgia is indicated to be present in 24% of gynaecological patients presenting with pelvic pain. This might represent another form of central sensitisation in women with pelvic floor dysfunction. It may present as a dragging sensation and pelvic pressure.

Women with CSSs or FSSs have high symptom bother with such symptoms of prolapse compared with women without CSSs.

These conclusions appear to support the hypothesis that women presenting predominantly with a dragging sensation / pelvic pressure but not a vaginal bulge could have underlying FSS or CSS contributing to their symptoms.

Surgery for prolapse is usually considered after conservative management has failed and when the degree of bother or symptoms of the prolapse are perceived to be greater than the risks of surgery. Owing to increased bother, women with evidence of CSS might request treatment for prolapse at a stage of descent that would typically be considered less significant e.g. stage 1 on POP-Q.

Studies have demonstrated that if a patient carries a diagnosis of fibromyalgia, 35 % of women reporting a bulge will have the leading edge of the prolapse within the hymen i.e. not thought to be clinically significant (Adams K et al., 2014). Surgery might not improve the bulge or pressure sensations in these patients and could lead to a "mismatch" between patient and physician expectations. Without an understanding of this mechanism, such patients may undergo additional surgical procedures without a successful outcome.

There may be a time critical component to successful surgery: requiring intervention before the onset of enhanced pain response (Petersen KK et al., 2015b). For example, those patients with pain after revision surgery may have continued enhanced temporal summation within the central nervous system as compared with patients without pain

(Skou ST et al., 2013) resulting in exacerbation of more diffuse pain after further surgery (Skou ST et al., 2014a).

The current state of understanding has raised several questions including:

- What is the impact of CSSs in the development of chronic postoperative pain after prolapse surgery?
- What is the role of CSSs in predicting the success of surgical treatment for prolapse?
- Could dragging sensation be one of the symptoms seen in patients with CSSs?
- Does identifying and understanding CS/CSS help patients to have more realistic expectations from treatment and prevent disappointments?
- Is CS a useful conceptual construct for explaining reduced surgical success in those with CSS?
- How should the perioperative management strategies be optimised in the presence of CSSs? i.e. how do you choose the right treatment for the patients with CSS? Is there a downregulatory cascade i.e. is there any way by which the heightened pain response can be downregulated or minimised?

The aim of this study is to enable us to explore in depth some of these questions. The study consists of five parts as following:

- To capture the awareness of central sensitisation and CSS amongst gynaecologists and allied health professionals dealing with women with pelvic organ prolapse.
- To identify the proportion of women having evidence of CSSs presenting with different gynaecological disorders. Before conducting this part of the study, factor analysis of CSI was undertaken in our cohort to decide whether a total score or a subset should be used to identify women with CSS.

- To conduct a systematic review and a critical appraisal of literature on clinical outcomes of surgery in patients with CSS
- To compare the outcome of pelvic organ prolapse surgery in women with and without evidence of CSSs.
- A qualitative study of patients with CSS who've feel they have had a poor outcome following surgery i.e. with persistent or new symptoms. The purpose of the interviews will be to explore a patient's perception of the effectiveness of surgery for their condition.

Chapter 2 – A survey on "Awareness of Central Sensitivity Syndromes and Central Sensitisation amongst gynaecologists and healthcare professionals dealing with pelvic organ prolapse."

Abstract-

Background-

Central sensitisation (CS) has been found to contribute to many unexplained medical symptoms as in functional somatic disorders or central sensitivity syndromes (CSS). The clinical management of these group of patients can become quite challenging due to lack of awareness of coexisting CSS. This study aims to capture the awareness of CS/CSS amongst health professionals dealing with pelvic organ prolapse (POP).

Method:

This was a single point online survey of understanding about central sensitisation and its potential role in pelvic organ prolapse. The survey was undertaken in month of August 2017and sent to urogynecologists, gynaecologists (UK), to members of South Wales Incontinence group and General practitioners (Wales) by a single electronic mailing of the questionnaire. The responses were in either yes /no or in form of rarely, occasionally, frequently and always respectively.

Result:

A total of 70/200 (35%) responded to the survey. Thirty -four (48%) do not believe that there is an element of central sensitisation where the symptoms are out of proportion to the objective prolapse. Significant number (45%) of health professionals are unaware that patients with fibromyalgia or CFS or vaginal pain have high bother with their symptoms. Similarly, significant number of health professionals have not heard the term central sensitisation or Central sensitivity syndrome (CSS) (48.5%).

Conclusion

Our survey identified the gap in knowledge about CS among health professionals

dealing with pelvic organ prolapse (POP). It is clear that there is need for more understanding of CS/CSS and its role in POP

Key words: Central sensitisation, Pelvic organ prolapse, gynaecologists, awareness, survey

2.1. Introduction

Pelvic Organ Prolapse (POP) can profoundly affect a woman's quality of life. Around 1 in 12 women living in the UK report symptoms of pelvic organ prolapse (Cooper J et al., 2015). However, frequently clinicians come across a clinical situation where symptoms are out of proportion of objective prolapse. As mentioned earlier this discrepancy might be due to variation in the processing of sensory stimuli.

The suggested mechanism involves the augmentation of pain/dragging transmission secondary to a process known as central sensitisation (CS) which has been suggested to be a contributor to many unexplained medical conditions as in functional somatic disorders or central sensitivity syndromes (CSS) (Woolf CJ 2011). The issues with CSSs and central sensitisation might be overlooked by the clinicians due to lack of awareness regarding these conditions and this phenomenon (Kaur P et al., 2015). As a result, the management of these patients could be compromised with poor patient-reported outcomes leading to frustration and dissatisfaction amongst both clinicians and patients.

Although there is growing recognition of CSSs, variation exists in professional knowledge and understanding among different specialities of medicine. This forms the basis of the current survey distributed to general gynaecologists, urogynaecologists, continence nurse specialists, general practitioners and physiotherapists who manage women with Pelvic Organ Prolapse (POP).

The purpose of this study was to capture the awareness of the concept of central sensitisation and CSSs amongst healthcare professionals dealing with pelvic floor dysfunction including general gynaecologists, urogynecologists, continence nurse specialists, general practitioners and physiotherapists.

We hypothesise that there is -

1. Suboptimal awareness about the existence of central sensitisation amongst this group of healthcare professionals.
2. Suboptimal awareness of the increased bother with symptoms of pelvic organ prolapse in patients with Central Sensitivity Syndrome.

2.2. Method

This was a single point on-line survey of understanding about CS/CSSs amongst healthcare professionals dealing with pelvic floor dysfunction. The survey was sent to urogynaecologists, gynaecologists (UK), physiotherapists, continence nurse specialists and General practitioners (Wales) who were members of Wales incontinence group by a single electronic mailing of the questionnaire. Closed questions were used in an attempt to have a better response rate (O'Brien S et al., 2016).

The questions were designed by a group of sub-specialists urogynaecologists with assistance from a clinical psychologist and cover domains in which it was felt that there was a lack of understanding about CSS and central sensitisation. (survey questionnaire attached in appendix section: page 201)

For example, 1) Whether they have heard about central sensitivity syndromes and what are the common conditions contributing to the term central sensitivity syndrome. 2) Whether they see patients with symptoms of prolapse out of proportion to the objective prolapse. The responses were in a yes /no format and if a 'yes' response to elaborate whether this was: rarely, occasionally, frequently or always. Before rolling out the

survey, a pilot was undertaken in the local department to six health professionals including 2 gynaecology consultants, 2 physiotherapists, 1 continence nurse specialist and 1 obstetrics and gynaecology trainee. This was done to check that the related categories had been covered and to check for the understanding of the survey. Minor amendments were done to the final survey based on the responses. Survey Monkey was used to collate and analyse the responses to the questionnaire.

All questions and responses are listed in tables 1-7. The result was analysed on complete datasets following closure at 12 weeks after initial circulation. Two reminders were sent at 4 and 8 weeks after the initial circulation to all potential respondents. Statistical significance was calculated using one sample t-test. XLSTAT was used for statistical analysis.

2.3. Result

The initial invitation went to 200 healthcare professionals. A total of 70/200 (35%) responded to the survey. Of those 31% responded after initial circulation, 44% after the first reminder and 25% after the second reminder. The survey covered responses from both primary care (represented by GP's in the group) and secondary care. Out of 70 responses, 48 were gynaecologists with 22 being urogynaecologists, 13 were GP's, 7 were physiotherapists and 2 were continence nurse specialists (Table 1).

Thirty-three (47%) out of 70 responded that they encounter majority of the time with patients where the predominant complaint about prolapse is a dragging sensation rather than a bulge. (Table 2). Twenty-eight (40%) felt that they frequently see patients where symptoms are out of proportion to the objective prolapse (Table 3).

Thirty-four (48.6%) do not believe that there is an element of central sensitisation where the symptoms are out of proportion to the objective prolapse findings and 10 (14.2%) do not know (Table 4). A Significant number (32/70 -45.7%) of healthcare

professionals were unaware that patients with fibromyalgia or CFS or vaginal pain have higher bother with their symptoms than those without these conditions (table 5). Similarly, a significant number of healthcare professionals had not heard the term Central Sensitisation or Central sensitivity syndrome (CSS) (48.6%). (Table 6)

Table 1: Showing the response to Q1- Describe your role.

Role	Number-70 (100%)
Gynaecologist with a special interest in urogynaecology	16 (22.9%)
Subspecialist urogynaecologists	6 (8.6%)
General Gynaecologists	26(37.1%)
Physiotherapist	7(10.0%)
Continence specialist nurse	2(2.8%)
General practitioner	13(18.6%)

Table 2: Showing the response to Q2-How often do you see patients with pelvic organ prolapse complaining of dragging sensation rather than bulge?

Frequency	Number(n-70)
Rarely (once in 2-3 months)	15(21.5%)
Occasionally (once in a month)	22 (31.5)
Frequently (every week)	28 (40%)
Almost always (every patient)	5 (7%)

Table 3: Showing the response to Q3- In your practice how often do you see patients whose symptoms of prolapse are out of proportion to/ with the degree of prolapse?

Frequency	Number (n-70)
Rarely (once in 2-3 months)	16 (22.8%)
Occasionally (once in a month)	26 (37.2%)
Frequently (twice in a month)	25 (35.7%)
Almost always (every week)	3 (4.3%)

Table 4: Showing the response to Q4- Do you believe that there is an element of central sensitisation in women where their symptoms are out of proportion to the objective prolapse?

Yes	26(37.2%)
No	34(48.6 %)
Do not Know	10 (14.2%

Table 5: Showing the response to Q5- Do you believe that women with Fibromyalgia, chronic fatigue syndrome, ME or some vaginal pain have worse symptoms than women who do not have these conditions?

Yes	38 (44.3%)
No	4 (5.7%)
Do not Know	28 (40%)

Table 6a: Showing the response to Q6 'a' - Have you heard the term central sensitivity syndrome?

Yes	36 (51.4%)
No	34 (48.6%)

Table 6b: Showing the response to Q6b -Please circle the following conditions that can contribute to central sensitivity syndrome

Conditions	responses
Fibromyalgia	8
Chronic fatigue syndrome	47
Migraine	3
Anxiety	0
Depression	5
Neck whiplash injury	0
Temporomandibular joint dysfunction	0
All of the above	13

Table 7: Showing responses amongst different health care professionals for questions 2-6

			Q 2			**Q 3**			**Q4**			**Q5**		**Q6**	
	Occ (n-22)		Frequently(n-28	Always(n-5)	Occ (n-26)	Frequently(n-25)	Always (n-3)	Yes n-26	No n-34	Do not know n-10	Yes n-38	No n-4	DNK n-28	Yes n-36	No n-34
Subspecialist (n-6)	x		3	3	x	4	2	5	1	x	6	X	X	6	x
With special interest (16)	2		12	2	7	8	1	10	5	1	15	1	x	15	1
Generalist (26)	11		4	x	11	3	x	6	19	1	9	2	15	4	22
Physiotherapist (n-7)	2		5	x	2	5	x	5	1	1	6	1	x	6	1
Continence nurse specialist (n-2)	1		x	x	1	1	x	x	x	2	X	X	2	x	2
GP (n-13)	6		4	x	5	4	x	x	8	5	2	X	11	5	8

The group of physiotherapists and urogynaecologists within the group were more aware of CSS/CS compare to other groups (GP, general gynaecologist and incontinence nurse specialist). (Table 7)

As shown in table 7 urogynaecologists seems to have more awareness about CS compared to other groups but the number were small. To eliminate the risk of under coverage bias we conducted another survey to British Society of Urogynaecologist (BSUG). The society is a nationally accredited society for urogynaecologists and hence, allows us to capture a wider perspective about patients with pelvic floor dysfunction.

The BSUG research committee approves the survey and the timing of survey and I was allowed to conduct the survey in the month of October 2018. By this time, I had some preliminary results from the cross-sectional study. Hence, thought of repeating the survey with 3 additional questions. These questions were added in order to help us identify the areas of future research regarding management of women with pelvic floor

dysfunction and CSS. The questions were designed in the MDT group involved in the care of patients with pelvic floor dysfunction at Singleton Hospital, Swansea. The group involved, continence nurse advisor, Urogynecologists, physiotherapist and psychologist. Additional questions were as follows-

1. Do you feel that there is a need of understanding the role of CS in pelvic floor dysfunction?. The responses were in the form of Agree, Disagree, neither agree or disagree.

2. Do you think we should screen patients for symptoms suggestive of CSS'S before offering Pelvic Organ Prolapse surgery? The response were in the format of yes/no and not sure.

3. Do you think that patients with CSS should have a trial of other treatment strategies such as myofascial release, Cognitive Behavioural therapy or using neuromodulators eg gabapentin before pelvic organ prolapse surgery?

The survey was piloted again within the department with these extra questions before submission to the BSUG research committee.

After the pilot, the survey was submitted to the BSUG research committee for their approval. The research committee checks the appropriateness of the questions and topic of the survey. Once the survey was approved, it was sent out to the BSUG members by the BSUG administration staff via the survey monkey link. Two reminders were sent at 6 and 10 weeks before the survey was closed in 12 weeks. Total 61 responses were received. The survey confirmed the results of the previous survey. Although, majority of them felt that women with FM, CFS or ME have worse symptoms, only 52% believed that there is underlying central sensitisation (CS) or heard the term CS. Majority (72%) agree that there is need of understanding of the role of CSS's/CS in pelvic floor dysfunction. However, only 32% believed that we should routinely screen for CSS and offer them alternate treatment before pelvic organ prolapse surgery. (Table 8-10)

Table 8: Showing response by BSUG members to question- Do you feel that there is a need of understanding the role of CS in pelvic floor dysfunction

Response	Total no-61
Agree	44(72.13%)
Disagree	3 (4.92%)
Neither agree or disagree	14(22.95%)

Table 9: Showing response by BSUG members to question- Do you think that we should screen for symptoms suggestive of CSS'S before offering Pelvic Organ Prolapse surgery ?

Response	Total no-61
Yes	20(32.79 %)
No	18 (29.51%)
Not Sure	23 (37.70%)

Table 10: Showing response by BSUG members for question- Do you think that patients with CSS should have a trial of other treatment strategies such as myofascial release, Cognitive Behavioural therapy or using neuromodulators eg gabapentin before pelvic organ.

Response	Total no-61
Yes	19(31.15%)
No	12(19.67%)
Not Sure	30 (49.18%)

2.4. Discussion

Our survey demonstrated that a significant number of healthcare professionals dealing with pelvic organ prolapse encounter women where their symptoms of prolapse are out of proportion to the objective prolapse. A significant proportion of them were not aware that women with conditions such as fibromyalgia or CFS, may have increased bother with their symptoms of pelvic organ prolapse and nearly half of them are unaware of the terms Central sensitisation or Central Sensitivity Syndrome.

Patient management and treatment choices are based on an understanding of the disease or disorder patterns. In the absence of this, the symptoms and distress for the patients can persist. This can impact adversely on patient well-being as well as the patient-doctor relationship. (Marianne R et al., 2017).

It has already been established that women with fibromyalgia, CFS, (CSSs) seek interventions at a stage which is clinically less significant than those without these conditions due to increased bother from their symptoms (Adams K et al., 2014). In these women, a lack of understanding of the underlying CSS conditions can lead to misdiagnosis and as a result inappropriate and ineffective therapies including surgical intervention. For example- such women can have pain in other parts of the body such as the bladder, bowel, and pelvic floor muscles with or without evidence of pathology e.g. endometriosis and end up with multiple laparoscopies and/or hysterectomy.

Managing patients and their expectations where symptoms are inconsistent with the observable pathological findings can be challenging. Some might consider surgery to be the appropriate treatment and so awareness of the phenomenon of central sensitisation and presence of underlying central sensitivity syndromes by clinicians might help to focus on treatment strategies which are less invasive and potentially provide a better outcome e.g. those related to the central nervous system such as medication, exercise, mindfulness, and cognitive behavioural therapy. This might also avoid unnecessary surgery (Barron K 2017) with its attendant risks and possibly improved patient satisfaction.

Raising awareness about Central Sensitivity Syndromes should be widened to include not only pain specialists who regularly manage patients with these presentations but also other relevant clinical disciplines including GP, surgery, and gynaecology. This is of great significance, as chronic pain patients often are unable to comprehend why a

relatively minor trauma (such as localised knee/ shoulder injury or perineal repair) or in some having no confirmed trauma can result in disabling pain. Explaining that the pain system is a dynamic system which undergoes changes, can help the patients to have a better understanding of their current situation (Arendt-Nielson L et al., 2018). This can also help the clinician to offer appropriate treatment strategies.

The strength of our survey is that this is the first survey (to our knowledge) to explore the understanding of CSS among Gynaecologists and other healthcare professionals.

The main limitation of the survey is that the numbers are small and possibly unrepresentative of all clinicians. Because of low response rate there is an element of under coverage bias . There may be also a geographical effect on the responses of the clinician as there can be variation in the complexity of cases encountered by clinicians (some areas see more complex cases than others). Also, the results showing contradictory responses may be due to the fact that some clinician esp primary care physicians and continence nurse specialist may not manage women with pelvic organ prolapse and refer them to see specialists in first instance. In order to eliminate these shortfalls, we repeated the survey with the urogynaecologists (who routinely manages women with pelvic organ prolapse) nationally. However, we still need further survey to assess global awareness amongst the health care professionals managing pelvic floor dysfunction.

2.5. Conclusion

Our survey appears to have identified a gap in knowledge about Central Sensitivity Syndromes and phenomenon of central sensitisation amongst clinicians and other health care professionals managing women with pelvic organ prolapse. It is clear that there is a growing need for more understanding of central sensitivity syndromes and its relevance to patient's symptoms as lack of it might affect decision making and the outcome of treatment. Understanding about CSSs might enable different management

strategies and reduce unnecessary surgical intervention. The survey has also identified the need of future research to assess the effect of downregulation of central sensitisation in symptoms of pelvic floor dysfunction.

Future research ideas- 1. To conduct the survey amongst members of International and European Urogynaecology Society to assess global awareness of CSS/CS in healthcare professionals dealing with pelvic floor dysfunction.

Chapter 3a - Factor analysis of CSI in a cohort of women attending Gynaecology outpatient Department (GOPD)

Abstract- This part of the study aimed to perform a factor analysis of CSI in a cohort of women presenting in GOPD with various gynaecological problems to reveal the underlying structure in this cohort. Factor analysis of the CSI collected from the period of March 2014 to June 2014 from patients presenting in GOPD at University Hospitals Plymouth NHS Trust was conducted. 333 questionnaires were evaluated. The results of this part of the study supported the use of the total cut off score rather than subset scores.

3a.1. Introduction

As alluded to in the literature, Central Sensitization (CS) refers to the amplification of neural signalling within the central nervous system (Woolf, 2011). Various mechanism have been described such as dysregulation of ascending and descending tracts in the CNS (Yunus 2007, Heinricher et al., 2009), overactivation of glial cells (Nijs et al., 2017), excess production of brain-derived neurotrophic factor (Phillips and Claw 2011) and dysfunction of the stress system (Van Houdenhove & Luyten, 2009). Initially, CS had been considered as an explanatory mechanism in Fibromyalgia but now has also been proposed to be responsible for chronic pain in other patients with evidence of tissue trauma or pathology e.g. multiple sclerosis (Fernandez-de-las-Pefias et al., 2015), Osteoarthritis (Akinci et al., 2016) and post-surgical breast pain (Fernandez -Lao et al 2011) as well as in conditions where the pain is not the dominant symptom, such as in – post-traumatic stress disorder, multiple chemical sensitivities, restless leg syndrome (Yunus, 2015) and overactive bladder (Reynolds et al., 2016). Yunus described these latter groups of disorders collectively under the umbrella term Central Sensitivity Syndromes. It was also evident in the literature that various other symptoms such as insomnia, feeling "unrefreshed" after sleeping, difficulty concentrating, some bladder or bowel problems and fatigue are frequently noted within these disorders (Yunus, 2015).

As well as these aforementioned co-morbid symptoms, psychiatric disorders, emotional symptoms (anxiety and depression) and childhood abuse experiences are associated with CSS (Phillips and Clauw., 2011). Thus, the CSI was developed incorporating many of these features/symptomologies.

The CSI was originally composed to screen symptoms suggestive of the presence of CSS (Mayer et al., 2012). The items of this inventory were evolved from an extensive literature search around somatic and emotional health-related symptoms found in these conditions. It contains a heterogenous list of 25 questions (widespread pain, sleep disturbance, digestive and urologic symptoms etc). The CSI has been validated in various languages such as English, French, Serbian, Gujrati, Dutch, Spanish and Brazilian. However, factor analysis in these different languages has yielded conflicting results. Factor analysis has been undertaken of the original version developed in English in a cohort of subjects having chronic musculoskeletal pain disorder. This determined 4 factors (domains) with 3 items not loading to any of the factors. It has been suggested that the overall score, and not the scores of any individual domain is most appropriate for use.

This study aimed to conduct a factor analysis of CSI in our cohort of women with gynaecological conditions presenting in the Plymouth gynaecology outpatient department to have a better understanding of the patient's symptom presentation to draw specific patient profiles based on these domains and also to consider whether a particular domain can be used for screening instead of a total score.

3a.2. Method

This was a prospective study conducted at a tertiary University hospital and was approved by the West of Scotland Research Ethics Committee. The study was conducted from March 2014 to June 2014. All women attending GOPD and were above the age

of 18 were included in the study. Women who were not able or willing to consent were excluded. The patient information leaflet was sent to all women before the clinic appointment. All women were asked to complete a validated Central Sensitisation Inventory (CSI) (see pg. 30) whilst they were in the clinic waiting area prior to their appointment**.**

Factor analysis was then conducted on the collected CSI. This is a statistical method to reduce a collected dataset into a set of measurement variables (domain scales) based on correlations (Meyer et al 2012). To evaluate the suitability of data for factor analyses, the Kaiser-Mayer-Olkin measure of sample adequacy and the Bartlett test of Sphericity was used and to produce the results comparable to that original reported by Meyer (Meyer et al 2012), a principal component analysis (PCA) was carried out using oblique PROMAX rotation. Items obtaining a factor loading of >0.4 were retained and the number of suggested domains were indicated by components achieving Eigenvalue (raw sum of the squares) of 1 or more. The cut off for the loading was set at 0.4. Cronbach's alpha coefficient which reflects the average intercorrelations among items was used to test internal consistency. The acceptable value being reported between 0.70-0.90

SPSS version 26.0 was used to conduct the statistical analyses

3a.3. Results

Three hundred and thirty-three questionnaires were completed. The majority of the items did not have questionable univariate normality based on their skewness and kurtosis values (Table 11). The items obtained a corrected item-total correlation that was higher than the rule of thumb" minimal value of 0.25 (Devellis RF, 2006)

The Kaiser- Mayer-Olkin (KMO) test revealed a coefficient of 0.895 and the Bartlett test of sphericity demonstrated the figure of 2072.120(p 0.000) indicating the sampling

adequacy was excellent and confirming that the correlation matrix was suitable for factor analysis.

Table 11: Showing descriptive statistics for the factor analysis of CSI.

	N	Minimum	Maximum	Mean	Std. Deviation	Variance	Skewness	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error
I1	331	.00	4.00	2.1752	1.05577	1.115	-.138	.134
I2	331	.00	4.00	2.1631	1.17961	1.391	-.097	.134
I3	328	.00	4.00	.8476	1.02025	1.041	.987	.135
I4	327	.00	4.00	.9572	1.18192	1.397	.846	.135
I5	330	.00	13.00	1.7879	1.38725	1.924	1.691	.134
I6	326	.00	4.00	.6350	1.10044	1.211	1.612	.135
I7	329	.00	14.00	.9301	1.39620	1.949	3.182	.134
I8	328	.00	4.00	1.8750	1.20127	1.443	.051	.135
I9	328	.00	4.00	1.0915	1.21315	1.472	.868	.135
I10	329	.00	4.00	1.7356	.97216	.945	.170	.134
I11	329	.00	4.00	1.4438	1.21626	1.479	.408	.134
I12	330	.00	4.00	2.1212	1.19669	1.432	.011	.134
I13	328	.00	4.00	1.6646	1.08522	1.178	.308	.135
I14	327	.00	4.00	1.5902	1.28594	1.654	.365	.135
I15	328	.00	4.00	1.7043	1.21448	1.475	.160	.135
I16	329	0	4	1.64	1.093	1.194	.185	.134
I17	330	.00	4.00	1.9091	1.12889	1.274	.027	.134
I18	332	.00	4.00	1.8283	1.30212	1.696	.016	.134
I19	330	.00	4.00	.6879	1.01785	1.036	1.369	.134
I20	328	.00	4.00	.5793	.97042	.942	1.734	.135
I21	323	.00	4.00	2.2724	1.24115	1.540	-.284	.136
I22	325	.00	4.00	1.7323	1.34682	1.814	.169	.135
I23	327	.00	4.00	1.6850	1.05458	1.112	.168	.135
I24	309	.00	4.00	.5210	1.01469	1.030	1.894	.139
I25	319	.00	4.00	1.5141	1.31236	1.722	.322	.137

Table 12: Showing total Eigenvalues and variance of each item of CSI

	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total
1	7.357	29.428	29.428	7.357	29.428	29.428	5.143
2	1.625	6.501	35.929	1.625	6.501	35.929	3.465
3	1.282	5.129	41.058	1.282	5.129	41.058	3.511
4	1.231	4.924	45.982	1.231	4.924	45.982	2.560
5	1.086	4.345	50.327	1.086	4.345	50.327	1.583
6	1.029	4.116	54.443	1.029	4.116	54.443	3.499
7	.966	3.865	58.308				
8	.891	3.563	61.871				
9	.857	3.427	65.298				
10	.801	3.203	68.501				
11	.788	3.153	71.654				
12	.754	3.015	74.669				
13	.685	2.740	77.409				
14	.661	2.644	80.054				
15	.639	2.555	82.609				
16	.612	2.449	85.059				
17	.555	2.219	87.277				
18	.524	2.095	89.372				
19	.493	1.971	91.343				
20	.467	1.867	93.210				
21	.433	1.733	94.942				
22	.368	1.472	96.414				
23	.346	1.385	97.799				
24	.282	1.127	98.926				
25	.268	1.074	100.000				

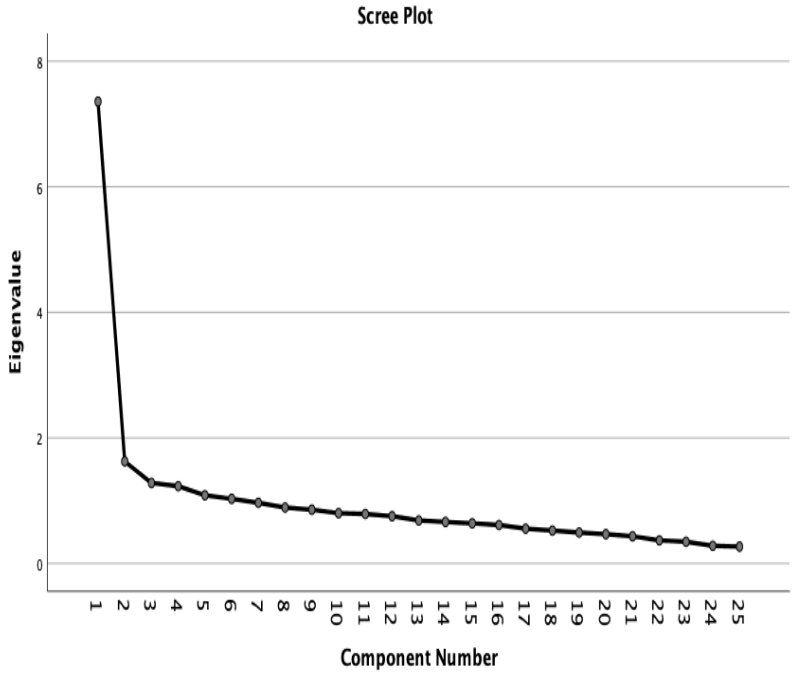

Figure 3: Showing scree plot for various items on CSI related to Eigenvalue.

The analysis revealed 6 factors with eigenvalues >1 which accounted for 54.43% of the variance. The first component elucidated 29.42% of the variance, whereas the other 5 components interpreted 6.5%, 5.12%,4.9%,4.3% and 4.116% respectively. The eigenvalues of 6 components were 7.35, 1.62, 1.28, 1.23, 1.08 and 1.02 (Table 12). However, the Scree plot suggested that 2 factors were clearly forming the basis of CSI. (Figure 3). These two methods (eigenvalue and scree) produce different suggestions. We looked at 6 factors, on the basis that 2 would not explain enough of the variance demonstrated.

Secondary analysis after oblique PROMOX rotation revealed 6 factors with the majority of items loading onto 4 factors and 4 questions not loaded to any factor (table 13).

Table 13: showing items loaded onto factors. (F-factor, I-item no of the questionnaire)- Pattern Matrix.

	F1	F2	F3	F4	F5	F6	No factor
I1			.805				
I2							x
I3						.552	
I4				.670			
I5							x
I6		.887					
I7		.542		.464			
I8	.576	.410					
I9		.531					
I10	.565						
I11					.715		

I12			.,721				
I13							x
I14	.711						
I15	.762						
I16	.605						
I17	.627						
I18			.460				
I19				.760			
I20				.641			
I21					.758		
I22		.430	.405				
I23		.474					
I24						.708	
I25							x

The items included in each factors are: Factor 1 (8,10,14,15,16,17), Factor 2 (6,7,8,9,22,23), Factor 3(1,12,18,22), Factor 4 (4,7,19,20), Factor 5 (11,21) Factor 6 (3, 24). This further suggest that there are only 4 strong factors and Factors 5 and 6 are rather weak 'factors' which may be due to not having enough questions relating to these latter two factors.

Based on the analysis following domains have been identified (depending on the items loaded) –

1. Factor1 – General physical symptoms ranging from 0.57-.76 (item 8 "I get tired easily) to item 15 "Stress makes my physical symptoms worse"

2.Factor 2 -CS-related symptoms

3.Factor 3- sleep disturbances

4.Factor 4- predominant temporomandibular

5 Factor 5- urological

6 Factor-6 psychological. History of abuse (from 0.55- 0.70 “I have anxiety attacks” to “I suffered trauma as childhood”

The internal consistency reliability analysis yielded values (Cronbach’s alpha) between 0.884-.894. Regarding, item-total correction, all values were above >.4 except for item 5 (I have problem with diarrhoea or constipation), Item 10 (I have headaches) Item 21 (I have to urinate frequently) and Item 24 (I suffered trauma as a child) where the values were 0.34, 0.338, 0.285 and 0.259 respectively (represents the values if these items were removed) (table 14). This might infer that these symptoms are not directly related to CS and need further evaluation.

Table 14: Showing item-total correlation of CSI

Item-Total Statistics

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
I1	33.3750	215.874	.411	.890
I2	33.3824	208.370	.606	.886
I3	34.7059	216.740	.423	.890
I4	34.5809	214.385	.412	.891
I5	33.7757	213.628	.347	.893
I6	34.9191	213.469	.487	.889
I7	34.7316	214.027	.453	.890
I8	33.7022	205.376	.665	.884
I9	34.4963	206.037	.663	.884
I10	33.8382	219.273	.338	.892
I11	34.1765	213.260	.438	.890
I12	33.4375	213.088	.439	.890
I13	33.9118	210.870	.585	.887
I14	33.9559	211.585	.430	.890

I15	33.8640	206.856	.619	.885
I17	33.6471	207.904	.643	.885
I18	33.6912	210.354	.473	.889
I19	34.8051	214.667	.466	.889
I20	34.9632	218.043	.401	.891
I21	33.3051	217.969	.285	.894
I22	33.8493	209.021	.504	.888
I23	33.8787	212.742	.523	.888
I24	34.9926	221.151	.259	.893
I25	34.0662	212.055	.433	.890
I16	33.9485	211.289	.565	.887

3a.4. Discussion

There has been increasing interest in that central sensitisation might be accountable for many conditions collectively termed as CSS. Various tools were used in literature in an attempt to screen patient symptoms suggestive of central sensitisation. The tools included the Sensory hypersensitivity scale (Dixon et al 2016), Pelvic pain convergence criteria (Levesque A et al., 2018) and the CSI. However, CSI is to date the most widely validated tool used for screening of patients with symptoms suggestive of CSS. The psychometric properties of CSI have been validated in a cohort of chronic pain patients. During the process of validation, these studies have also evaluated its factor model but produced conflicting results. We conducted this study to determine the scale structure and internal reliability in a cohort of women attending GOPD.

Our study has demonstrated a 6-factor model of CSI with 4 items (2,5,13,25) not loaded to any factor compared to the 4-factor model proposed in the analysis of the original English version of the CSI where 3 items (1,5and 14) not loaded to any factor(Mayer et al 2012). In our study, the questions loaded to each factor were also different compared to the original English version.

The results of our study, therefore, implies that a 21 item CSI remains and 4 items are not valuable in any domains however when working with a total score of CSI, there is no problem to implement these items as the original article by Meyer where items 1, 5, and 14 did not load sufficiently on any factor in the factor analysis still these items remained in that study (Meyer et al., 2012) and subsequent studies Such as the French version which was comparable to the English version of the CSI with 4 factors and same items not loading to any factors (Pitance et al., 2016), the Dutch version confirmed a 4-factor structure but with different items in each factor and 5 items not relating to any factor (Kruegel et al., 2016) and the Japanese version which established a 5-factor model (Tanaka et al., 2017). To eliminate this variation and to produce good quality evidence, a large multi-country study was undertaken pooling 1987 subjects in a single database. This study also produced 4 factors but at the same time recommended that the reliability of the four factors was too low to be recommended for consideration of individual domain (Cuesta-Vargas et al., 2017).

Because of this variation and poor reliability in the results of these factor analyses, for practical implications, it is advisable to continue the use of 25 item questionnaire and use total scores for the screening of the symptoms suggestive of central sensitivity syndrome. Thus, we have used total CSI scores with a cut off of 40 to screen patients with CSS's attending the Gynaecological outpatient department in the next part of the study. However, the factor structure may be helpful for clinicians where a specific assessment of CS problems is warranted so that specific treatment strategy can be adopted.

The results of our study have shown excellent internal reliability similar to other studies on CSI. (Mayer et al., 2012, Pitance et al., 2016, Kruegel et al., 2016)

The strength of this factor analysis is that:1 this is the first study to determine domains and internal reliability of CSI in women with gynaecological problems 2. Use of appropriate statistical analysis

The limitation of this study is that these domains were extracted in a cross-sectional manner. Secondly, there was no test-retest reliability analysis undertaken

In the future, these domains must be tested longitudinally in terms of test-retest reliability in the same cohort. Further studies are also required to measure a clinical change in these domains of CSI following treatment to assess whether this can be a useful outcome tool or not.

3a.5. Conclusion

The results of the above study demonstrate that total scores for CSI should be used for screening purpose.

Suggestion for Future Research

1. Comparing the surgical outcome after pelvic organ prolapse surgery in patients with CSS using scores for factor 5 (urological) vs total scores of the Central sensitisation inventory.

2. To assess whether an item (on dragging sensation or heaviness in the pelvis) can be added in the CSI that can be loaded on factor 5 as one of the possible symptoms of central sensitization and creating short-form of CSI to be used in this population

3. Assessing patient perception of CSI whether they find it bothersome or useful using a validated QQ-10 tool.

Chapter 3b- The proportion of women with central sensitivity syndrome in Gynaecology Outpatient Clinics (GOPD)

Abstract-

Patients in Gynae outpatient clinic (GOPD) may present with symptoms not correlating well with the observed pathology and are usually labelled as having functional disorder or medically unexplained symptoms (MUS). Underlying central sensitivity syndrome (CSS) with central sensitisation (CS) as potential mechanism may be responsible for some of their symptoms. The aim of this study is to identify the proportion of women with Central sensitivity syndrome attending GOPD.

Method-

This was a prospective study conducted at University Hospital Plymouth NHS Trust between the month of March 2014-June 2014. All women attending GOPD included in the study were asked to complete a validated Central Sensitisation Inventory (CSI). The responses were graded on Likert scale from 0 (never) to 4 (always). Total score ranges from 0 to 100. For screening purpose, a single cut-off score of 40 of the CSI was used to identify the group of women who may have syndrome of central sensitisation.

Result - Three hundred and twenty-six women participated in the study. Overall, 123 (37%) women achieved a score above 40. This could be interpreted as at an increased risk of underlying central sensitisation. Out of these, 43 had earlier confirmed diagnosis of migraine, 55 (44%) had depression, 39(31.7%) had anxiety, 11 had fibromyalgia (FM), 34 had confirmed diagnosis of Irritable Bowel Syndrome(IBS) and 16 had Chronic fatigue syndrome(CFS/ME).

Conclusion-

Managing patients and their expectations in gynaecological outpatient departments, when symptoms are inconsistent with observable pathological findings, is challenging. This is further complicated when patients have a concomitant Central Sensitivity Syndrome which can also influence surgical outcome. Identifying these patients is a key factor for appropriate management.

Key words-

Central sensitivity syndrome, central sensitisation, pelvic organ prolapse, gynaecology outpatient clinic.

Summary-

Central sensitivity syndrome influences the outcome of any treatment and identifying this is a key factor for appropriate clinical management

3b.1. Introduction

Patients presenting in gynaecological outpatient departments frequently have symptoms which are not consistent with observable pathology. Some will have persistent pain which is disproportionate to the pelvic pathological changes noted and on a more thorough evaluation, will also have other more generalised symptomology such as fatigue, poor sleep pattern and perceptual sensitivities. This requires clinical vigilance particularly when patients are keen on definitive symptom relief despite modest clinical findings. Patients will often be distressed during the consultation, highlighting impaired dysfunction which they feel needs to be addressed by more aggressive management e.g. surgery. Anecdotally, many request hysterectomy in the belief that this will be beneficial.

Whilst it is common in primary care to manage patients having no clear diagnosis there has been little evaluation of the prevalence of this problem in secondary care. Historic evidence (Nimnuan C et al., 2001) suggests that over 50% of those attending secondary

care clinics do not have a clear diagnosis resulting in disappointment and frustration for both patient and clinician and the potential for ineffective treatments.

Patients can often find themselves being referred for further medical opinions particularly if there have been previous unsuccessful attempts at surgical resolution.

Such patients may or may not have a pre-existing diagnosis of a functional disorder including fibromyalgia, chronic fatigue syndrome (CFS) or myalgia encephalitis (ME), medically unexplained symptoms (MUS), Central sensitivity syndromes or more regionally based diagnoses such as irritable bowel syndrome and interstitial cystitis/painful bladder syndrome. These are overlapping diagnoses, which are inconsistently used and there is continued debate about the aetiology and conceptualization of these various functional disorders. One diagnostic label which appears to be acceptable to both clinicians and patients is Central Sensitivity Syndrome (CSS) (Yunus MB, 2008).

Recent research studies have shown that surgical intervention is less effective in those with a central sensitivity syndrome and potentially might exacerbate the symptoms in some e.g. shoulder pain (Gwilym SE et al., 2011).

There is currently little evidence clarifying the prevalence of a central sensitivity syndrome among women presenting to a gynaecological outpatient's department especially with pelvic organ prolapse. This study was, therefore, designed to estimate the proportion of women who might have symptoms suggestive of a central sensitivity syndrome attending with pelvic organ prolapse compared with women with general gynaecological conditions.

3b.2. Method

This was a prospective study conducted at a tertiary University hospital and was approved by the West of Scotland Research Ethics Committee. The study was conducted from March 2014 to June 2014. All women attending gynaecology out- patient clinics

and were above the age of 18 were included in the study. Women who were not able or willing to consent were excluded. The patient information leaflet was sent to all women before the clinic appointment. All women were asked to complete a validated Central Sensitisation Inventory (CSI) (see pg. 30) whilst they were in the Gynaecology clinic awaiting their appointment.

For screening purpose, a single cut-off score of 40 of the CSI was used to identify the group of women who might have central sensitivity syndrome (Neblett R et al., 2013). To obtain a clinically significant value of CSI score, Neblett compared the CSI scores between the CSS patient group and non- patient group using ROC analysis. The score of 40 on the CSI provided good sensitivity (81%, to correctly identify CSS patients) and specificity (79%).

Due to variation and poor reliability of the results of factor analysis, it's not recommended to use the individual domains of CSI to screen patients with CSS. This was also confirmed in our study (see chapter 3a). The CSI was also not used to classify conditions based on the severity level.

3b.3. Sample size and statistical analysis

Following STROBE recommendations (An international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies), a formal sample size estimate for the survey was conducted. For the overall population, a sample of 300 would give a precision of the point estimate for the proportion with CSS of between 3.4% and 5.2% with a two-sided 95% CI and expected proportions of 10% and 30% with CSS. The CSI scores were calculated from the individual question responses using cut-off of 40 to define CSSs. Proportions and confidence intervals were calculated using SPSS version 17. Fisher's exact test was used to calculate p value.

The CSI scores for pelvic organ prolapse (POP) patients were also then compared to those with other general gynaecological diagnoses including menorrhagia, pelvic pain, ovarian cyst, request for sterilization, overactive bladder, intermenstrual bleeding, post-menopausal bleeding, cervical polyp and endometriosis.

The comparison of CSI scores was performed between the POP group and other general conditions to understand whether a dragging sensation (one of the symptoms of pro-lapse) is attributed to presence or absence of CSS which might subsequently help in comparing the outcomes of surgical treatment of prolapse (see chapter4). Two sample Kolmogrov-Smirnov test/Two tailed test was used to compare the distribution of CSI scores in women with evidence of CSS and pelvic organ prolapse and in women with evidence of CSS and other gynaecological conditions using XLSTAT.

3b.4. Results

About 480 women attended gynaecological clinics during this period. Three hundred and twenty-six women participated in the study. Overall 123 (37%) women achieved a score above 40 suggesting underlying CSS. Out of these, 43 had earlier confirmed di-agnosis of migraine, 55 (44%) had depression, 39(31.7%) had anxiety, 11(25%) had FM, 34(27.6%) had confirmed diagnosis of IBS and 16 (13%) had CFS/ME. These conditions were identified from the CSI and were found to be in a combination of 2-3 in women with CSI scores between 40-60. Women (25%) with high CSI scores (60-91) were found to have a combination of 4-5 conditions. This might suggest that higher scores are reflecting the presence of more conditions coming under the umbrella of CSS and so more symptoms.

Out of 326 women, the main complaint of 86 women that attended the outpatient clinic was pelvic organ prolapse, while 240 women attended with other gynaecological symp-toms. The evidence of central sensitivity syndrome was established in 27 women (32%)

with pelvic organ prolapse and 96 women (40%) with other gynaecological conditions (table 15).

The other general gynaecological conditions referred were menorrhagia, pelvic pain, ovarian cyst, request for sterilization, overactive bladder symptoms, intermenstrual bleeding, postmenopausal bleeding, cervical polyp, endometriosis, fibroids, lichen sclerosis, women for Fenton's reverse perineorrhaphy and, women referred for management of menopausal symptoms. The CSI scores for the general gynaecological conditions (excluding pelvic pain) were the range of (18-54). The CS scores for pelvic or vaginal pain were in the range of (32-91). There were 2 cases of known endometriosis and the scores were 59 and 60 respectively.

Table 15: Showing evidence of central sensitivity syndrome in women with pelvic organ prolapse and other gynaecological conditions in outpatient clinics

Total no-326	Pelvic Organ Prolapse- n-86	Other Gynaecological conditions. n-240	Fischer test
With CSS.n-123	27(32%)	96(40%)	
Without CSS.n-203	59(68%)	144(60%)	P=0.25

Mean CS scores for the pelvic organ prolapse group and other gynaecological conditions were 33.9(SD 15.2) and 37.2 (SD 15.8) respectively. There was no statistical difference in overall mean central sensitisation scores between women with pelvic organ prolapse and other general gynaecological conditions (table 16). However, women presenting with pelvic or vaginal pain were found to have higher central sensitization scores($p<.001$) whether they are in POP group or General Gynae group (table 17,18).

*Table 16: Showing mean central sensitisation scores and *standard deviation between women with pelvic organ prolapse and other general gynaecological conditions.*

Conditions	Mean CS score	t test
Pelvic Organ Prolapse	33.9 (*SD-15.2)	*p=0.098

Other Gynaecological conditions	37.2 (*SD-15.8)	

*Table 17: Showing mean CSI scores and *standard deviation in patients with general gynae condition with pain compared to those without pain.*

Conditions	Mean CS Score	t test
General gynae condition without pain	34.6 (*SD 14.9)	P=0.000
General gynae condition with pain	53.6 (*SD 15.6)	

*Table 18: showing mean CSI scores and *standard deviation in patients with pelvic organ prolapse with pain compared to those without.*

Conditions	Mean CS Score	t test
Pelvic organ prolapse without pain	32.47 (*SD 15.06)	P=0.000
Pelvic organ prolapse with pain	48.5(SD 16.8)	

The mean CSI score in women with POP with established evidence of CSS was 51.81(SD-9.11) and mean CSI score in other gynaecological conditions with evidence of CSS was 52.7(SD-10.43) (Table 19). The distribution of CSI scores in patients with evidence of CSS in both groups is shown in graph1(fig 4) and graph 2 (fig 5) respectively. Two sample Kolmogrov-Smirnov test/Two tailed test used to compare the distribution, demonstrate that both groups follow very similar distributions (p value 0.998).

*Table 19: Showing mean central sensitisation scores and *standard deviation in women with evidence of CSS.*

Conditions	Mean CS Score
Pelvic Organ Prolapse	51.81(*SD-9.11)
Other Gynae Conditions	52.7(*SD-10.43).

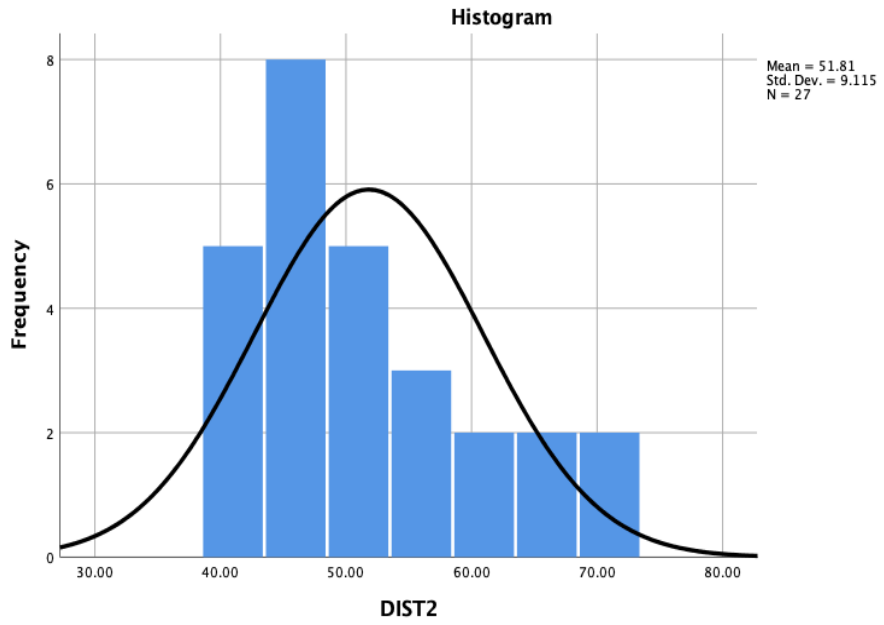

Figure 4: Graph 1- Distribution of CSI scores in patients with pelvic organ prolapse and CSS. The X axis shows the CSI scores and Y axis is the frequency of these scores.

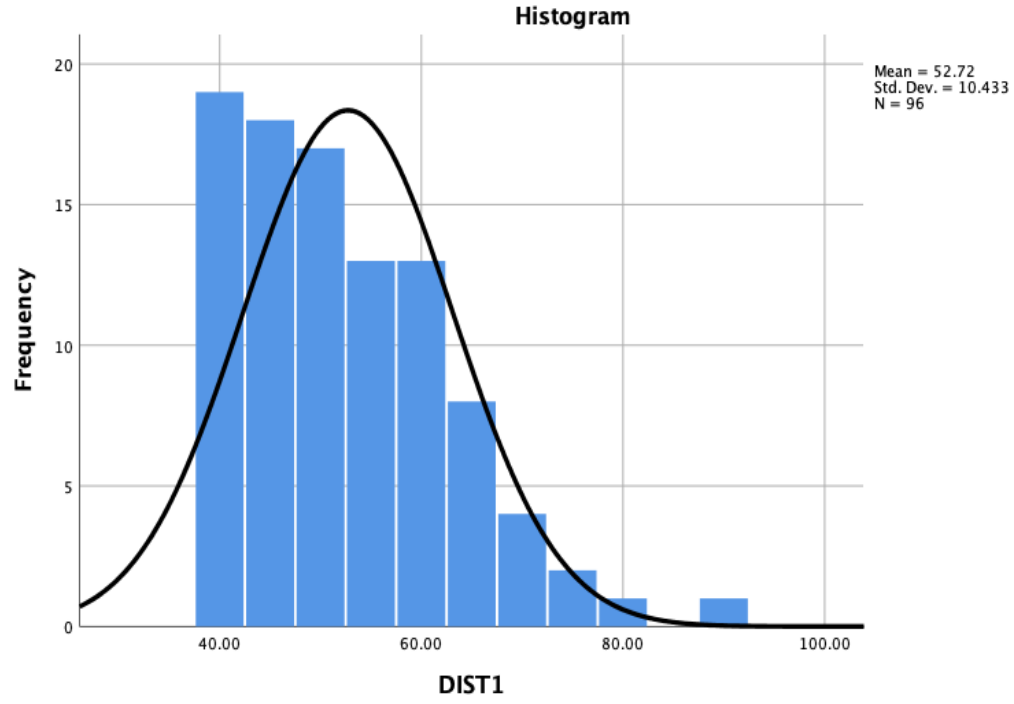

Figure 5: Graph 2- Distribution of CSI scores in women with General Gynae Condition and CSS. The X axis shows the CSI scores and Y axis is the frequency of these scores.

3b.5. Discussion

Clinicians will often assess patients who experience somatic symptomology which does not fit the clinical findings. Some of these patients will have a clinical label of

"functional disorder" with the symptoms not demonstrably due to a specific underlying disease process (Engel GL1977). Research indicates that the widespread symptomology may be due to a dysfunction in central processing and possibly peripheral processing (Bourke JH et al., 2015).

Central sensitisation is a plausible theoretical explanation the persistence of such symptoms. Previously the term Medically Unexplained Symptoms (MUS) was used but was often felt to be unhelpful to both patients and clinicians and could result in disengagement by the patient with the perceptions that the clinician thought that "the symptoms were all in their head" (Sharpe M 2013).

A potentially more acceptable 'umbrella' term that is being increasingly adopted is central sensitivity syndrome (CSS). This includes conditions such as fibromyalgia, IBS, Temporomandibular joint disease (TMJ), chronic fatigue syndrome, tension headache/ migraines, restless leg syndrome, multiple chemical sensitivities, interstitial cystitis, myofascial pain syndrome, post-traumatic stress disorder (PTSD) and neck injuries such as whiplash (Yunus MB, 2007).

The patients suffering from this syndrome often have higher symptom bother due in part to underlying central sensitization (Adams K et al., 2014; Shin Hyung K et al., 2015). As discussed in the literature review, the development of this syndrome can also result in considerable psychosocial impairment, work disability, and increased utilization of health care resources (Creed FH et al., 2012, Barsky AJ et al., 2001; Shraim M et al., 2013).

The clinical challenge is to recognize, diagnose and manage this syndrome since it can be detrimental to the patient-doctor relationship as well as put patients at risk of unnecessary diagnostic and surgical interventions (Fink P., 1992; Warren JW et al., 2014; Flynn TW et al., 2011). It is thought that some patients can potentially lose trust in the

medical system as they perceive medical disbelief in their presentations while clinicians might consciously or unconsciously, develop negative attitude towards them.

It is, therefore, imperative to identify patients with evidence of central sensitivity syndrome during the clinical decision making, provide a detailed explanation to the patient and ensure appropriate interventions.

This part of the thesis explores the extent of CSS within the gynaecological arena. Our study has demonstrated that around 37% of patients attending our general gynaecological outpatient clinics (32% with POP and 40% with other Gynae disorders) could be considered as having a central sensitivity syndrome when using a validated CSS instrument. The CSI scores in both groups followed very similar distributions. The study indicated that women with pelvic pain and vaginal pain had higher scores on the CSI. This supports the potential pathophysiological role of central sensitization in chronic pelvic pain, irritable bowel and bladder pain syndrome where the symptom complex is out of keeping with the clinical presentation as suggested by other authors (Neblett R et al., 2013).

The strength of this study is that it is the first study to our knowledge to identify women having evidence of central sensitivity syndrome presenting with pelvic organ prolapse and general gynaecological conditions. This might have implications for the poor outcome of surgical intervention for POP (Olsen AL et al., 1997) as has previously been seen in patients with shoulder pain (Gwilym SE et al., 2011).

The weakness of this study is that there is no objective test utilized to identify CSS and so a specific independent measure cannot currently be used with confidence. The presence of a central sensitivity syndrome is based on a questionnaire only; however, the CSI has been validated and tested for its reliability in diagnosing CSS (Mayer TG et al., 2012; Kregel J et al., 2015; Yunhee C., 2013).

There is very little in the literature to assess the role of CSSs for the outcomes of surgery for POP. This is addressed in the next part of the thesis.

3b.6. Conclusion

Managing patients and their expectations in gynaecological outpatient clinics, when symptoms are inconsistent with observable pathological findings is challenging. This is further complicated when patients have a concomitant Central Sensitivity Syndrome which might influence surgical outcome. Further research is required to elucidate the way this syndrome is best understood and managed in the gynaecological arena.

Suggestion for Future research- A Longitudinal study to assess the role of pregnancy and delivery on CSI scores and development of central sensitisation.

Chapter 4- Clinical outcomes of surgery in patients with CSS; a systematic review and review of literature

4.1. Introduction

As alluded to earlier, Fibromyalgia and medically unexplained symptoms (MUS) result in significant psychosocial impairment, work disability, and increased health care utilization by patients. The term FSS/ MUS has been largely fallen out in favour of another umbrella term Central Sensitivity Syndromes (CSS's). Previous research studies have demonstrated that patients suffering from these conditions have higher symptom bother than those without. Invasive options are often performed in these patients, with a higher risk of unexplained suboptimal results. This systematic review aims to establish, through the available literature whether the presence of Central Sensitivity Syndromes or Functional somatic disorders (described in chapter 1) influences the clinical postoperative outcome.

4.2. Method-

The study design is based on "PICOS"(see below) and follows the PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses)

PICOS:

Participants (P)

This review will consider all studies that involve patients who underwent any type of surgery

Intervention (I)

Diagnosis of CSS /FSS/FM/CFS/MUS/CS/ME /central sensitisation

Comparison- (C)

Patient without CSS/FSS/FM/MUS/CFS/ME

Outcome measure (O)

The outcomes of interest are quality of life (QOL), patient satisfaction, complications, physical functioning, length of hospital stay and recovery following surgery

Types of Studies (S)

case series, retrospective studies, observational studies, open-label studies, randomized clinical trials, systematic reviews and meta-analyses

4.3. Exclusion criteria-

Articles in another language than English, commentaries, letters to the editor and bio-mechanical studies and studies with pain as primary clinical outcome were excluded.

The reason for excluding pain as the primary outcome was that the thesis focussed on pelvic organ prolapse and pain (as opposed to heaviness and dragging) is not a symptom of prolapse. Secondly, we analysed the symptom improvement, effect on the quality of life (as primary outcome) with patient satisfaction and patient global impression of improvement (PGI-I) following prolapse surgery in patients with CSS (in the next part of the study) and focussed on any literature available on these clinical postoperative outcomes.

4.4. Search Strategy

Database search included PubMed, Medline, Embase, Web of Science and Ovid database Only articles written in English were selected. Database MeSH terms used were central sensitivity syndrome, central sensitization, fibromyalgia, functional somatic syndrome, medically unexplained symptoms, chronic fatigue syndrome, ME, surgical outcome post-surgical outcome, quality of life scores, patient satisfaction, length of stay and complications.

Literature was independently searched by me after receiving training from a member of the library team and then all search results were screened based on title and abstract by two authors (MV, AD). The full-text article was retrieved if the citation was

considered potentially eligible and relevant. In the second phase, each full-text article was again evaluated whether it fulfilled all criteria. If any of the eligibility criteria were not fulfilled, the article was excluded. Disagreements on inclusions and exclusions were resolved by discussion and did not require a third reviewer.

4.5. Data collection

The studies retrieved during the searches were entered into EndNote and then transferred to Covidence software for screening. In the first phase of screening, two researchers screened the abstracts of the retrieved for eligibility, and any conflicts were resolved after discussion.

All quantitative papers on post-surgical clinical outcomes, relating to complications, length of stay, readmission rates, QOL, and patient satisfaction in patients with central sensitisation, central sensitivity syndromes, fibromyalgia, chronic fatigue syndrome, migraine or the functional somatic syndrome were included. Papers, where the primary outcome was pain or postoperative opioid consumption, were excluded for the reasons mentioned above.

In the second phase of screening, each full-text article was evaluated as to whether it met all eligibility criteria. If any were not fulfilled, the articles were excluded.

Covidence software was then used to extract data from the studies selected for inclusion and to record the results of the assessments of the methodological quality of each paper, and both were used to create this final report.

Data were extracted for the following: (1) study design and purpose; (2) characteristics of the study population; (3) measured variable(s) of central sensitization and central sensitivity syndromes pre-surgery and method of assessment; (4) post-surgical outcome variable(s) regarding the length of stay, complications, readmission, patient satisfaction, physical function, and QoL and assessment method; (5) length of follow-up,

important results for this review such as correlation coefficient, risk ratio, odds ratio and information on the risk of bias.

As mentioned above, two reviewers independently performed the data extraction, and any controversies were resolved through discussion to reach a unanimous decision, therefore, did not require the third person

4.6. Risk of bias (quality) assessment

Covidence software was then used to extract data from the studies selected for inclusion and to record the results of the assessments of the methodological quality of each paper, and both were used to create the final report. An assessment of bias in the included randomized controlled trials was performed according to the guidelines laid out in the Cochrane Handbook for Systematic Reviews of Interventions, to give a clear idea of the strength of clinical indications (i.e. the role of CSS/CS on clinical outcomes after surgery) in this review (Higgins J et al 2011). Allocation, blinding, attrition, reporting, and other potential sources of bias were assessed using this approach. The Newcastle-Ottawa quality assessment scale was used for non-randomized observational studies to assess the quality. The protocol was submitted to the PROSPERO registry, registration number (CRD 42020165140).

4.7. Strategy for data synthesis

A narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics, type of outcome and intervention content was provided. The summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardised mean differences (for continuous outcomes), along with evidence of publication bias, is also provided

4.8 Results –

The figure (fig 6) demonstrates the selection process of this review. 16 studies were included in the qualitative synthesis. Most studies were excluded based on the population studied and the nature of the predictor.

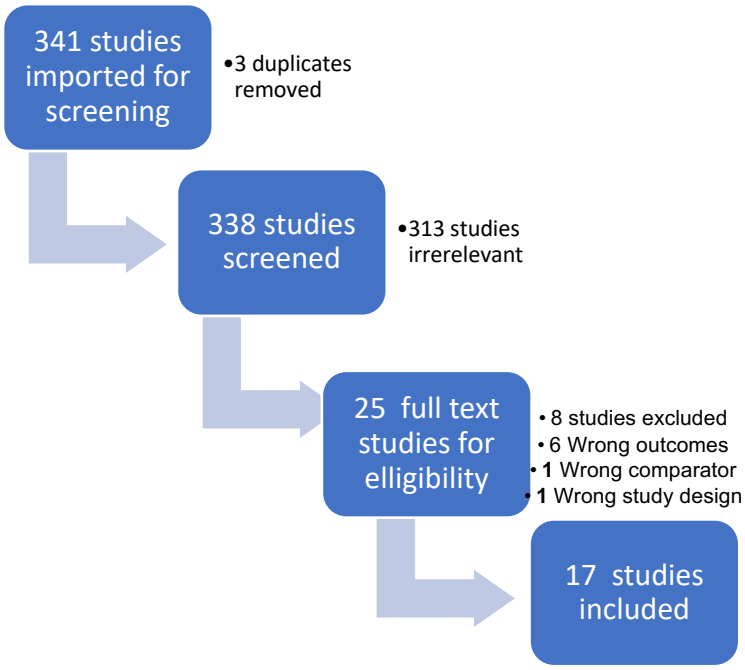

Figure 6: PRISMA Flow chart.

No Randomised controlled studies were found. There were no studies to evaluate the clinical outcomes following any gynaecological surgery. There was 1 systematic review, 8 case-control studies, 1 cross-sectional study and 7 cohort studies for review. (Table 20). The methodological quality of the studies is summarised in table-21,22. Meta-analysis was not undertaken due to high heterogenicity among the studies regarding study design and outcome measures.

Table 20: Showing all type of studies included.

Author	Study design	Sample size	Type of intervention	Outcomes	conclusion	Follow up
Soler et al 2008	Nested case-control analysis	283 patients, including 25 with FM and 258 without FM	Endoscopic sinus surgery	Assessment on QOL by Pre-operative RSDI, CSS scores And a change in these scores post-operative	Preoperative scores higher in patients with FM. Both groups showed improvement after surgery with no difference on QOL in patients with FM or without FM However, medication requirement was higher in the FM group	Average 11.7 mths (3-21) in the FM group and 14.7(6-21) in patients without FM
Bican et al., 2011	Prospective Case-control study	59 patients (90 knees) with FM matched with 59 controls	Total Knee Arthroplasty	Post-operative satisfaction and functional outcome using Likert scale and SF-36	FM patients were less satisfied with the surgery	3.4 yrs.
Gwilym et al., 2011	Prospective case-control	20 patients,17 patients selected with Shoulder Impingement syndrome matched with 17 controls who were free from shoulder pain with OSS of 48	Subacromial decompression	Primary outcome- Improvement in OSS scores and Secondary outcome- Diagnosis of Hyperalgesia by QST	Preoperative hyperalgesia had a significant role as a predictor of postoperative OSS (I.E presence of referred pain and a higher level of hyperalgesia were associated with worse outcome	3 months
D'Apuzzo et al., 2012	Retrospective cohort study	110 patients for TKA with FM (141 knees) 102 patients for final analysis	Total knee arthroplasty (TKA)	Knee Society Knee Score, Satisfaction Secondary outcome- postoperative complications	85 patients (108 knees) reported improvement (82%) however, patients with FM have a high prevalence of complications esp. arthrofibrosis (9%)	7 years (2-16 yrs.)
Bionna et al., 2013	Retrospective observational	286 patients including 18 with FM (5 underwent surgery-11 joints)	Orthopaedic evaluation for shoulder pain and shoulder surgery	Diagnosis of FM, new OSS, SF-12, and global SOD score	Fibromyalgia may be a cause of failure in the treatment of concomitant painful shoulder	15 months (range 12-27)

DeConde et al., 2014	Retrospective analysis of a prospective case-control study	225 patients with refractory CRS, 46 had a comorbid migraine and 186 were without migraine	Endoscopic Sinus surgery	RSDI, CSS, SNOT-22	Patients with comorbid migraine and CRS are more likely to have less severe evidence of disease and worse preoperative baseline QOL scores. Both groups demonstrated comparable improvement after surgery	Mean 6.3 months (6, 12 and 18 months)
Bennett EE et al., 2017	Retrospective cohort study	1404 patients out of which 788 had CSI scores 40 or more	Cervical and spinal fusion surgery	QoL measures-Patient Health Questionnaire-9 (PHQ-9); EuroQOL-5D index; Pain and Disability Questionnaire (PDQ)	High CSI score is significantly associated with worse QOL outcomes following cervical and spinal fusion surgery comparing to those with low CSI scores	6 weeks to 1 year
Roh et al., 2015	Prospective cohort prognostic study	93 recruited from 109 eligible patients	Surgical treatment for hand fracture	Post-op grip strength, total active range of motion and disability	Pre-operative high catastrophizing and anxiety were associated with weaker grip strength, decreased range of motion, and increased disability after surgical treatment for a hand fracture at 3 months. This effect was not seen beyond 6 months	3 and 6 months
Baert et al., 2015	Systematic review	Total 16 studies, 10 studies on function and 1 on QOL, patients between 43-241	Total Knee replacement	Presurgical pain modulation in the context of "cognitive-emotional modulation", WOMAC physical function questionnaire	Conflicting evidence for the role of depressive symptoms and anxiety in predicting knee function as well as for the role of pain catastrophising in predicting knee function. Limited evidence on the effect of depression on QOL after TKA and for coping strategies and knee function	6 weeks to 5 years
Ablin et al., 2017	The prospective observational cohort study	39 patients, 11 with FM and 28 without FM	Cervical or Lumbar laminectomy or foraminotomy	Change in WPI and SSS scores, SF36,	The negative correlation between presurgical severity of FM symptoms and postoperative SF36 and may have less favorable outcome after spinal surgery	10-12 weeks

De Groef et al., 2017	Cross-sectional study	274 patients who had surgery for breast cancer	Breast cancer surgery (mastectomy, lymph node dissection	Disability of Arm, Shoulder, and Hand (DASH) questionnaire, CSI	At long term, pain and central sensitisation contributes to upper limb dysfunction in breast cancer survivors	1.5 years
Nelson et al., 2018	Retrospective case-control	76,103 patients with FM compared with 76,103 without FM	Total Knee Arthroplasty (TKA)	Medical and implant complications, 90 days readmission rates	Increased risk of post-operative complications in patients with FM	90 days
Duckworth et al., 2018	Retrospective study	103 patients	Total Hip Replacement	Pain catastrophising and Oxford Hip Score (OHS)	Higher preoperative catastrophising tends to correspond with poorer improvements in OHS pre- to postoperatively.	12 Months
Leung et al., 2019	Prospective cohort study	243 patients with knee OA Outcome data in 232 patients at 6 months and 235 at 12 months	Knee replacement	Patient satisfaction at 4 and 6 months using a 4-point Likert scale WOMAC to assess pain and function concerning central sensitization measured by PPT at forearm	Preoperative central sensitisation was not statistically significantly associated with satisfaction	6 and 12 months
Donnally et al., 2019	Retrospective case-control review	9346 patients with FM with degenerative lumbar pathology and 9346 patients without FM	Primary 1 to 2 level posterolateral lumbar spine fusion	Readmission rate, length of stay and postoperative complication	Patients with FM had a higher rate of postoperative anaemia, pneumonia, cost of care and readmission	30 and 90 days
Moore et al., 2019	Retrospective case-control	152,755 patients with FM	TKA	Complications following TKA	patients diagnosed with fibromyalgia are more likely to develop several medical complications than non-fibromyalgia patients.	90 days
Lopiz et al., 2019	Retrospective case-control	293 patients, 26 with FM, 20 included (6 had no follow up) compared with 20 patients without FM	Isolated Arthroscopic Subacromial decompression (IASD)	DASH (Disability Arm Shoulder and Hand, constant score (CS), relative constant score (RCS), VAS pain score and patient satisfaction questionnaire	FM is a prognostic factor of a poor outcome after an IASD	36.8 mth(23-84 month)

4.9. Summary and comparison of the studies

The study by Soler et al (Soler MZ et al 2008) demonstrated no difference in QOL following sinus endoscopic surgery in patients with FM compared to those without FM in chronic rhinosinusitis condition (CRS). They assessed the quality of life scores by using the Rhinosinusitis disability index (RSDI) and the Chronic Sinusitis Survey (CSS). The RSDI measures rhinology health by way of 30 questions separated by physical, functional, and emotional subscales with possible scores ranging from 0 (lowest level of disease impact) to 120 (greatest level of disease impact). The chronic rhinosinusitis survey is an 8-week- duration monitor of sinusitis-specific outcomes comprised of six questions in two subscales (symptom and medication) with possible scores ranging from 0 (lowest level of functioning) to 100. A total of 283 patients were selected including 25 patients with FM. The control patients were matched 1:1 on potential confounding variables including gender, age (<3 years), and preoperative sinus opacification CT scores (<4). A total of 18 matched patients in each group were then compared. The study demonstrated that the patients with fibromyalgia were more likely to be women (96% versus 55%) and indicate clinical depression (48% versus 17%) but less likely to have nasal polyposis (8% versus 35%) than those without fibromyalgia. Patients with fibromyalgia were found to have less evidence of pathological changes such as sinus opacification on CT scan compared with patients without fibromyalgia. No significant differences were found in nasal endoscopy exam scores. Patients with fibromyalgia showed worse preoperative QOL responses compared with all other patients on the RSDI total (57.0 +/-16.6 versus 48.3+/- 21.4, $p < 0.05$), the RSDI functional subscale (18.1+/- 5.5 versus 15.5+/- 7.4; $p < 0.084$), CSS total (28.0+/- 17.0 versus 35.1+/-20.2; $p< 0.092$), and the CSS symptom subscale (18.3+/- 20.7 versus 28.9 +/-26.3, $p <0.053$).

Statistically significant improvements in QOL scores were noted in both fibromyalgia and non-fibromyalgia groups. For patients with fibromyalgia, mean RSDI total scores improved by 19.4+/-19.9 (*p<0.001).* There was also significant improvement seen in the CSS total score (22.4 +/-19.2; $p < 0.002$) as well as the symptom subscale (33.8+/-24.5; $p < 0.001$). Patients without fibromyalgia also showed significant improvements in all QOL domains except for the RSDI emotional subscale. There was no statistical difference in mean change for the RSDI total or subscale scores between the two groups. Similarly, there was no difference in the change score for the CSS total or symptom subscale between both groups. However, patients with fibromyalgia were shown to have less improvement in the chronic sinusitis survey medication subscale than patients without fibromyalgia (11.1+/-22.5 versus 28.2+/-23.9; $p< 0.027$).

Conclusion- This study showed that patients with comorbid CRS and fibromyalgia are more likely to be female, experience depression, and show worse baseline QOL scores when compared with everyone with chronic rhinosinusitis. Patients with fibromyalgia showed significant improvements in most sinus specific QOL measures following surgical intervention despite worse baseline scores. When compared with matched controls, these improvements were as great as those seen in patients without FM in nearly every sinus specific QOL measure studied.

The study by Gwillym (Gwillym et al., 2011) was aimed to investigate the evidence for augmented pain transmission (central sensitization) using QST (see chapter 1) in patients with shoulder impingement, and the relationship between pre-operative central sensitization and the outcomes following arthroscopic subacromial decompression using Oxford Shoulder score (OSS) of a single centre. They found that a significant proportion of patients awaiting subacromial decompression had referred pain radiating down the arm and had significant hyperalgesia to the punctate stimulus of the skin

compared with controls ($p < 0.0001$). The study also demonstrated that the presence of either hyperalgesia or referred pain pre-operatively resulted in a significantly worse outcome (in terms of OSS scores) from decompression three months after surgery (unpaired *t*-test, $p = 0.04$ and $p = 0.005$, respectively).

Ablin (Ablin et al., 2017) reviewed in an observational cohort study about the impact of FM symptoms on the outcome of spinal surgery. He analysed 39 patients, out of which 11 had FM and 28 had no symptoms of FM. 27 patients had lumbar spinal surgery and 12 had a cervical operation. They used the following validated instruments: Widespread pain index (WPI) and Symptom Severity scale (SSS) and the change in the various components of the SF-36(36-item Short-Form Health Survey questionnaire to assess QOL) to evaluate the association between fibromyalgia symptoms observed before surgery and the postoperative outcome. The SF-36 questionnaire was analysed according to the conventional method of eight components: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health. These components grouped into two sets: the physical component summary (PCS) and the mental component summary (MCS) with each component measured with a value ranging from 0 to 100, with 0 and 100 corresponding to the poorest and optimal health.

Overall, a significant 34% reduction in WPI (widespread pain) was observed post-surgically ($P < 0.01$), but no significant change was observed in SSS (symptom severity). Fibromyalgia syndrome (FMS)negative patients were found to have highly significant reductions of both SSS and WPI (-50.1% and -42.9%, respectively, $P<0.01$), while FMS-positive patients experienced no reduction of SSS symptoms (+3.6%, $p=0.76$) and only a marginally significant reduction in WPI (-20.3%, $P=0.04$). The study also demonstrated a significant negative correlation between results of presurgical WPI and

SSS and change in physical role functioning SF-36 component post-surgery(p=0.02) suggesting that patients with FM symptoms have less improvement in physical functioning after the surgery.

With regression analysis, the study demonstrated a difference in trend between FMS-positive and FMS-negative patients regarding postop changes in SSS, as well as a difference in trend regarding the general health role limitation due to emotional problems and pain components of the SF-36. Conclusions- Patients with symptoms typical of fibromyalgia may have a less favourable outcome after spinal surgery.

De Groef (De Groef et al 2017) and his team evaluated whether central sensitisation affects the upper limb function after breast surgery in breast cancer patients. They used CSI, Pain catastrophizing scale (PCS) and Disability of Arm, Shoulder, and Hand (DASH) questionnaires to assess the correlation between CS and upper limb dysfunction1 year following the surgery.The DASH consists of a 30-items, self-report questionnaire. Item responses range from 1 (no difficulty/no effort) to 5 (unable). Total scores range from 0 to 100, a higher score indicates greater disability. An impaired upper limb function has been defined as a score of 15 or more. Scores between 16 and 40 indicate a problem with upper limb function, whereas scores above 40 indicate that these patients are unable to work and the minimal clinically detectable change is 8 to 15 points for this questionnaire.

Two hundred and seventy- four (274) patients were analysed and the mean DASH score was 23. An impaired upper limb function (>15 on DASH) was reported in 170 (62%) of patients with 52 patients (19%) having a score above 40. The highest correlation was found for signs of central sensitization (mean score of CSI was 33) with a correlation coefficient of 0.615 (P<.001). Central sensitisation alone was found to be responsible for 40% of the variance in upper limb function. The mean score of the PCS scale was

10 with a correlation coefficient of 0.533($p < 0.001$) suggesting that patients with higher pain catastrophizing scores are at increased risk of impaired function following surgery. Conclusion- At long term, pain and central sensitisation contributes to upper limb dysfunction in breast cancer survivors.

The study by Blonna (Blonna D et al., 2013). evaluated retrospectively the prevalence of fibromyalgia in a cohort of consecutive patients attending the shoulder and elbow service of a single centre. Patients with a final diagnosis of fibromyalgia were 18 out of 286 (6.3%). These patients were subsequently asked to complete a validated shoulder questionnaire, the new Oxford shoulder (OS) score, quality of life questionnaire, the short form-12 (SF-12), and a global Summary Outcome Determination score (SOD score- a tool with a categorical and numerical component to compare surgical outcomes to presurgical states) (Blonna D et al., 2010). Authors found that, among the 18 patients with fibromyalgia, only five had already received a diagnosis of fibromyalgia or received a diagnosis of fibromyalgia during the first appointment, with the remaining 13 patients diagnosed during one of the follow-up examinations. Five patients had a total 11 surgeries. After an average follow-up of 15 months, 56% of patients reported having severe symptoms with the OS score and 44% had mild to moderate symptoms.

Based on the SOD score, one patient stated that the shoulder was worse than before the treatment, 56% of patients reported that shoulder symptoms were unchanged, 28% reported some improvement, and 11% reported great improvement. The average score was 1.3(-3 to 6) None of the patients reported that the shoulder was normal or almost normal. All of these patients reported mild to severe symptoms at the last follow-up.

Conclusions - Fibromyalgia could be the cause of failure in the treatment of concomitant painful shoulder

The study by D'Apuzzo and his colleagues (D'Apuzzo et al., 2012) demonstrated that patients with FM had higher postoperative complications such as arthrofibrosis following TKA surgery. Clinical outcome was assessed using the Knee Society Score pre and postoperatively, patient satisfaction (improvement, no improvement or worsening of symptoms) and the rate of postoperative complications.

110 patients with FM awaiting TKA were identified and 102 patients were included in the final analysis. The average age was 64yrs (39-86 yrs.) with a mean BMI of 33. Pt had TKA for degenerative joint disease, inflammatory arthritis, avascular necrosis, and post-traumatic arthritis. Eighty-Five (85) patients reported improvement and were satisfied with the surgery (82%). The Knee Society Score improved from an average of 60 to 84 postoperatively, however, this cohort of patients was found to have a higher rate of arthrofibrosis (9% -compared to 1.3-4.7% after primary TKA) followed by instability (12%) following TKA. This may be due to the baseline characteristics of these patients as found in the study by Hudson that 36% of FM patients had underlying hypermobility of joints (Hudson et al 1998). There are several limitations to this study such as the diagnosis of FM was difficult from chart review, no information on baseline laxity and information about physical examination of the knee following surgery available in only half cases making the overall quality of the evidence poor.

Similarly, Bican (Bican et al., 2011) and his colleague compared satisfaction and functional outcome following total knee arthroplasty in patients with FM to those without. They included 59 patients (90 knees). The majority of patients with fibromyalgia were women (57 patients, or 97%), with only two men (3%) in the cohort. The patients with FM were matched with one control based on type and date of surgery, diagnosis (osteoarthritis), fixation method, surgical approach, anaesthesia, surgeon, Charlson comorbidity index, age, height, and weight.

For evaluating pre- and postoperative functional status, as well as improvement in functional status after surgery, they utilised the SF-36 survey. Patient satisfaction was determined using the validated four-question 4-point (very dissatisfied, dissatisfied, satisfied and very satisfied. Responses scored as 0-100; 67 being satisfied, 100 -very satisfied). Fibromyalgia patients were less satisfied with the surgery overall than the control patients ($p = 0.0042$). There was a significant difference between the groups across all four dimensions measured (pain relief [$p = 0.0018$), ability to return to daily activities ($p = 0.0062$), functional recovery ($p = 0.0280$), and overall surgery ($p = 0.0124$). FM patients had lower pre and post-operative SF-36 scores than those without FM. Preoperatively, patients with FM were found to have lower scores in 4 out of 9 component scores i.e. body pain, general health, vitality, and social functioning as well as overall scores. Postoperatively, patients with FM had lower scores in seven of nine components i.e. physical role, body pain, general health, vitality, social functioning, emotional, mental health and overall scores ($p = 0.0104$, $p = 0.0006$, $p = 0.0064$, $p = 0.0068$, $p = 0.0031$, $p = 0.0119$, $p = 0.0061$ and $p =0.0013$ respectively). There were comparable changes in SF-36 scores in both groups following surgery however, there was no significant difference between the two groups ($p=0.08$). Conclusion- Although patients with FM were less satisfied with the surgery, they appear to show improvement in respect of function compared to those without the following surgery.

Donnally (Donnally JC et al., 2018) compared the postoperative complication rate, hospital readmission rates and hospital cost in patients with FM who had L1, L2 spinal fusion surgery for the degenerative lumbar spine. 9346 patients with FM were compared to 9346 patients without FM. Patients were identified from a national database and those with current spine trauma, infection, metastasis of the spine, revision fusion surgery, three-level or greater surgeries, concomitant cervical, thoracic, anterior lumbar

fusion, or posterior/transforaminal lumbar interbody fusion were excluded. They were matched based on age, sex, race, region, and the comorbidities such as acquired immune deficiency, body mass index (BMI), chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes, hypertension, hyperlipidaemia, systolic dysfunction, and tobacco use using Charlson Comorbidity Index (CCI).

77% of patients were females giving a 3.3:1 female to male ratio. During the first 30 postoperative days, patients with FM had higher rates of acute post haemorrhagic anaemia (0.52% vs. 0.20%, OR: 2.58; P < 0.001). This may not be important in the clinical context as the rate of transfusion was not significantly elevated compared to controls (0.32% vs0.20%).There was no statistically significant difference found in wound-related complications within first 30 days (0.19% vs. 0.23%, OR: 0.81; P = 0.520). During the first 90 postoperative days, the group found that patients with FM had significantly higher rates of pneumonia (0.43% vs. 0.12%, OR: 3.73; P < 0.001) and postoperative anaemia (1.03% vs. 0.37%, OR: 2.79; P<0.001). The rates of DVT (0.12% vs. 0.12%, OR: 1.09; P=0.832), and need for blood transfusion (0.32 vs. 0.20%, OR: 1.58; P1⁄40.113) were not significantly different.

Patients with FM had greater 30-day readmission rates compared to patients in the control group (RR: 1.23; P 1⁄4 0.007). No difference was found in 90-day readmission rates between the two groups. Both groups had an equivalent length of stay (3.60 vs. 3.53 days; P < 0.08). However, the postoperative cost within the first 90 days was 1.24% higher for patients with FM (P<.001). Conclusion- Primary 1- to 2-level lumbar fusions performed on FM patients have higher rates of postoperative anaemia and pneumonia as well as increased overall cost of care and increased readmission rates which can be explained due to increased cost of intra-hospital workup and treatment of the complications.

Bennett demonstrated that higher pre-operative CSI scores are associated with worse QOL outcomes following cervical and spinal fusion surgery (Bennett EE et al 2017). They evaluated the relationship of preoperative central sensitization inventory (CSI) scores and QOL by evaluating Patient Health Questionnaire (PHQ-9), EuroQol-5D, and Pain Disability Questionnaire (PDQ) which assess depression, quality of life and post-operative function status resp. A higher score is associated with worse outcome for PDQ and PHQ-9 whereas for EQ-5D a low score is associated with worse outcome.

Total 664 patients were included and 374 patients had CSI score more than 40 and 290 patients had CSI score <40. They found that higher CSI score was associated with higher (worse) postoperative PDQ total score (P=0.02), higher (worse) PHQ-9 score (p=0.001) and lower (worse) EQ-5D index (p<0.001). For each 10-unit increase in CSI score, the average LOS increased by 6.4% (P - 0.035).

The study by Roh (Roh HY et al 2015) and his colleagues demonstrated a positive relationship between high catastrophising and anxiety with decreased grip strength and increased disability following surgery for hand fracture. The severity of the injury was assessed with the Hand Injury Severity Scale (HISS). They measured the catastrophising and anxiety using the Pain catastrophising scale (PCS) and pain anxiety symptom scale (PASS). The study demonstrated that catastrophic thinking (beta = -1.29, partial R2 = 11%, p =0.001) and anxiety (beta = -0.83, partial R2 = 7%, p = 0.007) was associated with decreased grip strength at 3 months, but by 6 months, only anxiety (beta = -0.74, partial R2 = 7%, p = 0.010) remained an important factor. Decreased total active range of motion was associated with pain catastrophizing (beta = -0.63 partial R2 = 6 %, p = 0.024) and anxiety (beta = -0.28, partial R2 = 3%, p = 0.035) at 3 months but not at 6 months. Similarly, increased disability was associated with pain catastrophizing (beta = -1.09, partial R2 = 12%, p <0.001) and anxiety (beta = 0.93, p=0.001) at 3

months and not at 6 months. Conclusion- Pre-operative high catastrophizing and anxiety were associated with weaker grip strength, decreased range of motion, and increased disability after surgical treatment for a hand fracture at 3 months. This effect was not seen beyond 6 months suggesting that the recovery might be delayed in these patients but overall, there was no difference in the long-term outcome. This is likely due to overcautious activity restriction in patients with ineffective coping strategies which may, in turn, lead to stiffness and delayed recovery.

The study by Nelson (Nelson S et al 2018) evaluated the postoperative outcomes in terms of readmission rate, postoperative complications and total global (90 days) care cost in patients with FM compared to those without following TKA. 76,103 patients were assessed in both groups. Patients with FM were found to have greater incidence of developing 90-day medical complications (2.88% *vs.* 1.43%; OR: 2.05, P<0.001) such as shortness of breath (OR: 3.38, 95% CI: 2.64–4.32, P<0.001), cerebrovascular accidents (OR: 3.27, 95% CI: 1.66–6.43, P<0.001), pneumonia (OR: 2.67, P<0.001), non-healing surgical wound (OR: 2.27, P<0.001), urinary tract infections (OR: 2.10, P<0.001), acute post-haemorrhagic anaemia (OR: 1.95, 95% CI: 1.70–2.25, P<0.001), thrombocytopenia (OR: 1.84, P=0.032), requiring transfusions (OR: 1.69, P<0.001), and acute kidney failure (OR: 1.58, P=0.005) compared to patients without

No statistical difference was seen in the rate of delirium (OR: 1.90, P=0.082), acute pancreatitis (OR: 1.76, P=0.100), deep vein thrombosis (OR: 1.22, P=0.183), postoperative wound infections (OR: 1.12, P=0.531), paralytic ileus (OR: 1.11, P=0.739), and pulmonary embolism (OR: 1.04, P=0.886) between the two groups.

Patients with FM were found to have a greater incidence and risk of (12.5% *vs.* 11.6%; OR: 1.71, P<0.001) of 90-day readmission rates with high total care cost ($71,081.10 *vs.* $70,969.65, P<0.001) compared to matched controls. The study is limited due to its

nature (database analysis study), where miscoding and noncoding by the providers could be a potential source of error. Additionally, analysis of a single insurer's data may not give a true cross-sectional depiction of FM.

Similarly, Moore (Moore et al 2019) compared the rate of medical complications following total knee arthroplasty (TKA) between patients with FM and those without FM. A total cohort of 305,510 patients was studied. Both groups had an equal number of patients i.e. 152,755 patients in each group. Overall, 5,537 medical complications were found among fibromyalgia patients compared to 2,889 among non-fibromyalgia patients (odds ratio (OR): 1.95, 95% CI: 1.86–2.04, P<0.001] compared to the matched cohort. Patients with FM were significantly more likely to have UTI (OR:2.08,p<0.001), thoracic or lumbar neurites or radiculitis (OR : 5.85, p<0.001), acute post haemorrhagic anaemia (OR: 1.56,p<0.001), respiratory complications such as SOB (OR: 3.02, p<0.001), pneumonia (OR- 2.17, p<0.001, lung disease (OR: 2.17, p<0.001), higher transfusion(0R : 1.69p<0.001), acute kidney failure (OR: 1.27, p<0.001), neuralgia neurites (OR : 5.29, p<0.001).

The results of the study by Moore are limited as they are based on the examination of a total data rather than on raw data, which may have the potential to loss of information and inability to analyse individual-level data. Moreover, Fibromyalgia is a risk factor for the development of medical complications following TKA. FM patients were found to have reduced respiratory muscle endurance, inspiratory muscle strength, and thoracic mobility (Forti et al., 2016) and these changes may be responsible for higher respiratory complications compared to controls. There is a significant relationship seen between levels of Ferritin, vitamin B12 and folic acid with the development of FM. Serum Ferritin levels were found to be usually lower in FM patients compared to those without.

(Ortancil O et al., 2010) This may explain why these patients are more likely to develop acute post-operative anaemia requiring transfusion

The study by Lopiz (Lopiz Yet al., 2019) and his team evaluated whether FM could have an adverse impact on the clinical outcome after isolated arthroscopic Subacromial decompression (IASD). They compared 20 patients with FM who had IASD with those without FM. The outcome was assessed using Disability Arm Shoulder and Hand (DASH), constant score (CS), relative constant score (rCS), VAS pain score (visual analogue scale). Patient satisfaction was assessed using a single 2-level question (The yes/no question, ‘‘Are you satisfied with the result of the surgery?’’)

Failure of the procedure was defined as persistent pain (VAS>3). Mean follow up was 36 months. The mean preoperative constant score among participants with FM versus the control group was 37 vs 42 (p = .16), the mean rCS was 49.2 vs 55.3 (p = .18), the mean DASH was 45 vs 32 (p = .02), and the mean VAS was 6.1 vs 5.3 (p = .05).

The only parameter in which significant preoperative differences were found between both groups was on the DASH outcome measure. A statistically significant improvement was seen on all the mean values of both groups compared with the mean preoperative values. However, the mean postoperative DASH was found to be significantly worse (i.e. higher score) among the patients in the FM group compared with the control group (38.9 vs. 20.7; p = .009). There were no statistically significant postoperative differences in the range of movement, strength, or pain between the FM group and the control group. The revision rate was 28% in FM group compared to 15% in the control group (p = .45). Eighty-five per cent of patients in the control group were satisfied with the surgery compared with 55% in the FM group (p=.03). Failure of the procedure based on pain was 60% in the FM group, and 30% in the control group (p = .056).

Although patients had significant clinical improvement (as shown by DASH scores), they were less satisfied with the surgery. This may be due to their different expectations from the surgery.

The systematic review by Baert and his team (Baert et al., 2015) evaluated whether the presence of altered central pain modulation pre-surgical influences outcome after total knee replacement (TKR) in patients with knee osteoarthritis (OA) and if so which indices of central pain modulation predict poor outcome after TKR. All studies included in their review were prospective cohort studies.

The Western Ontario and McMaster Universities Arthritis Index questionnaire (WOMAC) was the most commonly used questionnaire to measure pain, function and QoL. The five most frequently evaluated psychological features were depression, anxiety, pain catastrophizing, fear of movement and coping strategy. A score for each subscale was calculated and transformed into a 0-100 scale; with a higher score indicate worst symptoms. Various questionnaires such as the Beck Depression Inventory, the State-Trait Anxiety Index and the Spielberger Strait Trait Anxiety Inventory were used. Five studies incorporated in the review demonstrated that presence of presurgical depression relates to worse knee function 3 months (Faller et al., 2003), 6 months (Lopez-Olivo et al., 2011) and 1 year (Faller et al., 2003, Utrillas-Compaired et al., 2014, Hanusch et al., 2014) whereas 3 studies found no contribution to knee function at 6 weeks (Sullivan et al., 2009), 6 months (Riddle et al., 2010) or 12 months after surgery. Only 1 study analysed the effect on QOL, demonstrating worse QOL 1 year after surgery in patients with presurgical depressive symptoms. (Utrillas-Compaired et al., 2014). Seven studies evaluated the effect of anxiety and 1 demonstrated that high presurgical anxiety was associated with worse knee function (Hanusch et al., 2014) whereas rest of the studies found no significant influence on knee function at 6 months (Riddle et al.,

2010) or 5 years (Brander et al., 2007). Regarding the role of Pain catastrophizing: 2 studies in the review found a positive correlation between knee function and pain catastrophizing (Yakobov et al., 2014, Sullivan et al 2011) whereas 2 studies did not find any significant association (Sullivan et al., 2009, Riddle et al., 2010). Two studies investigated the role of coping strategies in predicting knee function after TKR (Lopez-Olivo et al., 2011, Attal et al., 2014). They found that less problem solving and more dysfunctional coping was associated with worse knee function at 6 months (Lopez-Olivo et al., 2011). Conclusion- There is conflicting evidence for the role of depressive symptoms, anxiety and pain catastrophizing in predicting knee function after surgery. The evidence relating to the effect of depression on QOL after TKA and for coping strategies and knee function is also limited.

The study by DeConde and his colleagues assessed the impact of migraine on the quality of life outcomes after endoscopic sinus surgery (ESS) (DeConde et al., 2014). They analysed 229 patients with medically refractory chronic rhinosinusitis (CRS) following ESS using disease-specific QOL surveys: Rhinosinusitis Disability Index (RSDI), the Chronic Sinusitis Survey (CSS), and the Sino-nasal Outcome Test-22 (SNOT-22). Forty-six patients had a comorbid migraine and preoperative and postoperative QOL was compared with patients without migraine (n =183). Patients with migraine and CRS were more likely to be female (63.0% vs 44.3%, P=0.023); have fibromyalgia (10.9% vs 8.2%, P =0.009), and depression (30.4% vs 14.2%P= 0.010); and be less likely to have nasal polyposis (P 5 0.003). These patients were found to have higher pre-operative RSDI (54,6 vs 46.7, p=0.025) and average SNOT-22 scores (68.9 vs 54,6, p=0.019). QOL in both patients with and without migraine improved significantly after ESS (P = 0.003) and by comparable magnitudes (P =0.062).

Conclusion: Patients with comorbid migraine and CRS are more likely to have less severe evidence of disease and worse preoperative baseline QOL scores. This may imply that patients with comorbid migraine seek surgical management earlier in the disease process. However, ESS provides comparable improvement for both patients with and without comorbid migraine.

The study by Leung (Leung et al 2019) did not show any relationship between central sensitisation and patient satisfaction following Knee replacement in patients with OA. Central sensitization was assessed by measuring Pressure pain threshold (PPT) using digital algometer at the forearm. 249 consecutive patients with severe knee osteoarthritis (KOA) for knee replacement surgery were included. Patients with other diagnosis and revision surgery, with cognitive impairment or dementia (established by the short portable mental status question), were excluded. PPTs were measured at two body sites: the index knee and the right forearm to provide evidence of peripheral sensitization (index knee) and central sensitization (forearm) resp. Assessment of central sensitization was undertaken at the mid-point between the wrist and elbow of the volar aspect of the right forearm (PPT forearm). All patients had no pain in their right forearm at the time of assessment. Satisfaction was assessed using a 4-point Likert scale (satisfied, somewhat satisfied, dissatisfied and somewhat dissatisfied). Pain, stiffness and physical function of the knee were measured using the self-administered Western Ontario and McMaster Universities Index (WOMAC). A score for each subscale was calculated and transformed into a 0-100 scale; with a higher score indicate worst symptoms.

At 6 and 12 months, 8.2% and 5.1% of patients were “very dissatisfied” or “somewhat dissatisfied” with the outcome of their KR. Among those who reported "satisfied", 40.6% had slight or no improvement in function (40.6%) at 6 months, with similar results at 12 months after KR. There was not enough empirical evidence to suggest any

association between the PPT arm with dissatisfaction (RR-0.99 at 6 months and RR-1.002, p-0.8 at 12 months) and dissatisfaction with percent change in WOMAC scores in terms of function (rr-1.020, p-0.177). There was also no statistically significant interaction between radiographic severity of KOA with PPT measured at both knee and forearm for change in WOMAC outcomes. Conclusion- Pre-operative central sensitization measured by handheld digital algometry was found not to be statistically significantly associated with satisfaction or improvement in pain and function after KR.

The study by Duckworth (Duckworth et al 2018) assessed the relationship with pain catastrophising Scale (PCS) with improvement in Oxford Hip Score following THR. They found that Preoperative PCS had a weak negative correlation with the postoperative change in the OHS (r=-0.248; P=0.0114) and the only statistically significant predictor of postoperative OHS was the PCS (P=0.0207). Conclusion(s): Preoperative PCS has a negative correlation with the change in OHS following THR, demonstrating that higher preoperative catastrophising tends to correspond with poorer improvements in OHS pre- to postoperatively. However, as there is no paper available to assess this directly, it is difficult to comment on the quality of evidence.

4.10 Summary of overall quality of studies

The quality of studies was assessed using Newcastle -Ottawa quality assessment score for cohort and case-control studies (table 21) and overall quality was scored according to Agency for Health Research and Quality (AHRQ), while the quality of the systematic review was assessed using the scale shown in Table 22

Table 21: Quality of studies using the Newcastle-Ottawa scale.

Study	Newcastle-Ottawa quality assessment score	Overall Quality acc to AHRQ standard
Soler et al., 2008	Selection-4, comparability-1, out-come-2	good
Gwillym et al., 2011	Selection-3, comparability-1, out-come-3	good
Bican et al., 2011	Selection-3, comparability-1, outcome 3	good
D'Apuzzo et al., 2012	Selection-3, comparability-0, out-come-3	fair
Bionna et al., 2013	Selection-3, comparability-0, out-come-2	poor
DeConde et al., 2014	Selection-3, comparability -2, out-come-3	good
Roh et al., 2015	Selection-2, comparability-o, out-come-3	poor
De Georff et al., 2017	Selection-2, comparability -0, out-come--1	poor
Bennett et al., 2017	Selection-3, comparability-0, outcome-2	poor
Ablin et al., 2017	Selection-2, comparability-0, out-come-3	poor
Nelson et al., 2018	Selection- 3, comparison-2, outcome-2	good
Duckworth., 2018	Only Abstract available	N/A
Donnally et al., 2018	Selection-4, comparability-1, out-come-3	good
Leung et al., 2019	Selection-3, comparability-0, out-come-3	poor
Lopiz et al., 2019	Selection-3, Comparability-2, out-come-3	good
Moore et al., 2019	Selection-4, comparability-2, out-come-3	good

The quality of systematic review by Baert et al., 2016 was good quality review assessed using the scale below- overall good quality

Table 22: Demonstrating the quality of the systematic review.

Criteria	Yes	No	Other (CD, NR, NA) *
1. Is the review based on a focused question that is adequately formulated and described?	y		
2. Were eligibility criteria for included and excluded studies predefined and specified?	y		
3. Did the literature search strategy use a comprehensive, systematic approach?	y		
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?	y		
5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?	y		
6. Were the included studies listed along with important characteristics and results of each study?	y		
7. Was the publication bias assessed?	y		
8. Was heterogeneity assessed? (This question applies only to meta-analyses.)	Not applicable		

4.11 Discussion

The goal of this review was to review the literature around the role of CSS in surgical outcomes in terms of patient satisfaction, length of stay, complications, physical function and QOL following surgery. There was no evidence available regarding these outcomes in gynaecological surgery (hence why this MD thesis was undertaken by using surrogate markers looking at outcome measures in other surgeries)

Most of the studies identified were in the shoulder, spinal and knee surgery. One systematic review, 8 case-control, 1 cross-sectional study, and 7 cohort studies were identified and the relationship of CSS with various outcomes were broadly categorised into 3 headings:

1. CSS and physical function and improvement in symptom score -

There was only one systematic review available to consider. The review indicated that there is conflicting evidence on the role of depressive symptoms, anxiety and pain catastrophizing in predicting post-operative knee function with limited evidence on the effect of depression on QOL after TKA and for coping strategies and knee function

The conclusion from this review is limited by the heterogeneity of the psychosocial predictors evaluated and varied outcome measures in the included studies.

As an example, several different instruments were used to measure depression- these included the Beck Depression Inventory, the Patient Health Questionnaire-935, the Patient Health Questionnaire-841, the Depression, Anxiety and Stress Scale. There was also variation in patient populations and patients' characteristics. There was wide variation in the length of follow up period amongst the included studies which can influence the results (6 weeks to 5 years). In some studies, the nature of confounders was different which made the comparison more difficult.

Six studies looked at the change in symptom score and physical function after surgery. Out of these, only two were case-control studies (Gwilym et al, Lopiz et al., 2019) and in general, non-randomized observational studies do not provide good quality evidence (Higgins J et al., 2011). These studies demonstrated that FM, evidence of CS and pain catastrophizing is associated with worse outcomes, however, the study by Blonna et al had no information on pre-operative Oxford Score and SF-12 scores and only 5 patients with fibromyalgia underwent surgery. Thus, robust conclusions regarding its influence on outcomes of surgery cannot be drawn from such limited data. Similarly, in the study by Roh et al, the questionnaires used (PCS, PASS) have not been specifically validated in a trauma setting thus reducing the validity of their usage in this setting. There was no long-term data on functional outcomes as there could be improvements in motion and grip beyond 6 months. A single questionnaire was used to assess function (DASH) and analysis does not include other factors such as several damaged structures, level of injury, associated nerve injury which may affect the function postoperatively. Overall, our confidence in the results of the studies included is low. The conclusion by Ablin et al is limited by a relatively small number of patients and a short period of follow up along with the inherent patient heterogeneity due to various surgical indications.

Future research should aim to have more studies (case-control) with more homogeneity and adequate sample size and follow up to achieve a stronger recommendation.

2. CSS and postoperative complication, readmission rates, and length of stay-

Three studies looked at the rate of postoperative complication, readmission, and length of study (2 case-control and 1 cohort study). All studies found a higher rate of post-operative complications in patients with FM. However, there are limitations in study design particularly with the study by D'Apuzzo. There was no information on baseline

tissue laxity and no diagnostic criteria were used to identify patients with FM and subsequently the majority of patients were satisfied with the surgery.

Although, the study by Donally was a large retrospective study and found a higher rate of postoperative anaemia in patients with FM, the differences in these rates were < 1% and may not be relevant in actual clinical context considering that this is one of the common risks in orthopaedic surgery. Also, there was no information on whether patients were on any medication before surgery which could affect bleeding such as SSRI.

The study by Moore (Moore et al 2019) has also some limitations. The study looked at the aggregated data rather than raw data and therefore is a possibility of a loss of some information. The short duration of follow up (90 days) is also a limitation since this would miss any medical complications that could arise outside of the 90-day window.

The study by Nelson is a database analysis study and the validity of such studies are dependent on accurate diagnostic coding and miscoding could be a potential source of error. Currently, about 1.3% of coding errors are seen in the Medicare population (Burrus MT et al 2015). Additionally, the population of FM may not be a true representative as it evaluated only one insurer's data Lastly, it did not consider other comorbid conditions and adverse events that may be present in this cohort and is underreported.

Although the studies included demonstrated a positive correlation between FM and postoperative complication such as pneumonia and postoperative anaemia and an indirect effect on increased readmission rates, length of stay and cost of treatment, the review identifies the need for further research in which all the possible risk factors are assessed and controlled for to reach strong evidence in this area.

3. CSS and QOL and patient satisfaction following surgery

Two studies demonstrated that high CSI scores and PCS scores are related to worse QOL and improvement following surgery (Bennett et al 2015, Duckworth et al 2018).

However, study by Bennett is a poor-quality study due to its retrospective nature and no comparator with a selection bias. It is difficult to comment on quality and evidence of Duckworth study as only abstract is available.

One study demonstrated that patients with FM were less satisfied with the surgery (Bican et al 2011). The main limitation of this study is that it is a small cohort study and lacks published information on the severity of fibromyalgia, duration of its treatment, and the preoperative psychological status of the patients

Three studies did not show any difference in QOL following surgery between patients with and without FM. All of these studies showed comparable improvement in symptoms in both groups (Soler et al 2008, Leung et al 2019, Deconde et al 2014). The study by Leung and his group whilst having a large number of patients included only a single measure for CS (QST) and also did not include other predictors such as pain catastrophizing and fulfilment of expectations. Also, the result of this study should be interpreted carefully as 1. the sample size in this study was underpowered to demonstrate a statistically significant association between PPTs and KR outcomes. 2. PPTs, measured using a handheld digital algometer, have little predictive value as it measured a single static QST parameter and does not measure dynamic QST parameters and 3. The authors did not include other predictors of CS such as pain catastrophizing or depression. The study by Soler had an overall incidence of FM patients as 9% and there is a possibility that they may have missed some patients with FM as only those who had a previous diagnosis of FM were included. The review concluded that there is conflicting evidence on the impact of CSS on QOL and patient satisfaction after surgery.

It is increasingly acknowledged that satisfaction is one of the important but complex concepts to assess post-surgical outcomes as there is a shift in paradigm in patents care towards greater involvement of the patient in decisions regarding their treatment.

(Kitson et al 2013). Also, it is important to meet the expectations and needs of the patients. To meet the requirement of this shared decision-making process clinicians should be aware of the factors responsible for poor post-operative recovery. Despite the difficulty of how to interpret and measure patient satisfaction, it is recognized to be an indicator of the quality of care. (Jaensson M et al 2019). Therefore, well-designed studies are required to provide robust and valuable evidence on the role of CSS on patient satisfaction following surgery

The strengths of this review are that this is the first systematic review to evaluate the relationship between CSS and postoperative clinical outcomes in terms of patient satisfaction, QOL, complications, length of stay and physical functioning. The limitations of this review are that it has not included studies with pain as the primary outcome which can affect functioning and QOL indirectly and also there was wide variation in types of studies, outcome measures and length of follow up.

Despite these limitations, the results of this review have positive clinical implications. It does highlights that there is a need to pay greater attention to biopsychosocial considerations in surgical intervention to nurture better outcomes. If the identification of patients at risk of poor outcomes is evaluated early in the surgical assessment, potential suffering could be reduced by utilizing a broader therapeutic approach including that targeting desensitization of the central nervous system before considering a more invasive/ surgical approach.

4.12. Conclusion- The results of this systematic review demonstrate that limited evidence is currently available on the impact of CSS and CS on clinical outcomes of surgery. Overall, patients with FM and CS appear to have higher preoperative symptom severity and worse functional outcome with a higher rate of complications after surgery but the evidence on QOL and patient satisfaction is conflicting However, the relatively

limited evidence from this review does not suggest that presence of CSS/ fibromyalgia should be considered an absolute contraindication to surgical treatment. The evidence to date does suggest that the potential negative effects this syndrome can have on post-operative outcomes must be adequately explained to the patients so that expectations can be managed more realistically.

Future studies should be designed to specifically address the impact of CSS and CS on surgical outcomes specifically in the field of gynaecology since to date we have used data from other specialities as a surrogate marker. This is addressed in the next part of the study where we studied the role of CSS in pelvic organ prolapse surgery

Chapter 5 - A prospective cohort study to compare the outcomes of prolapse surgery between women with evidence of Central Sensitivity Syndrome (CSS) and women without CSS

Abstract-

Introduction- Pelvic organ prolapse has significant impact on quality of life. The lifetime risk of surgery for POP can vary from 11-20%. Conditions such as fibromyalgia, Chronic fatigue syndrome (CFS), Temporomandibular disorders collectively known as central sensitivity syndrome (CSS) may affect the outcome of surgery. The aim of this paper is to compare the outcomes of pop surgery between women with CSS and women without CSS.

Method- This was a prospective cohort study conducted between 2014-2017 at four centres (Plymouth, Bristol, Truro and Swansea) due to the training rotation of the researcher. Central sensitisation Inventory (CSI) was used to identify women with evidence of CSS. Subjective and objective outcomes following surgery were compared between two groups using POP-SS, EGGS, Pain scores and POP-Q. Non- parametric test was used for analysis.

Result- Total 78 women were recruited. Complete data was available in 62 patients. 23 patients were with evidence of CSS and 39 patients were without evidence of CSS. Women with evidence of CSS have higher pre- and post-operative POP-SS scores This was statistically significant (P- <0.0005, p-0.004). Seventeen (73.9%) women with CSS compared to 38 (97.4%) women without CSS demonstrated improvement of minimum 6 points on POP-SS scale. McGill's pain scores were higher in women with CSS both pre- and post- surgery.

95% of women without CSS achieved their goals and were satisfied with the surgery whereas, only 69.5% of women with CSS achieved their goals and were satisfied.

Conclusion- There is less favourable outcome of surgery in women with CSS especially in terms of persistence of symptoms, pain and overall satisfaction.

Key words-
Central sensitivity syndrome, pelvic organ prolapse, POP-Q, POP-SS (Prolapse symptom score)

5.1. Introduction

Pelvic organ prolapse (POP) is a frequent indication for hysterectomy and pelvic surgery and accounts for 15-18% of all hysterectomies. It is the most common indication for hysterectomy in postmenopausal women (Whiteman MK et al., 2008).

Pelvic organ prolapse is a complex condition with both functional and structural components to manage (Vitale SG et al., 2016) and therefore can have a significant impact on quality of life and psychological well-being (Hefni M et al., 2013).

According to the National Health Service (England) Hospital Episode Statistics (HES), the number of admissions for prolapse surgery was 1/1000 women in 2005 and 36% between 2008 - 2017 (see p.34/35).

The principal symptom manifested in prolapse is the perception of a bulge within the vagina (Barber MD et al., 2006). A significant proportion of women, however, may also complain of a dragging sensation or pelvic pressure (Barber MD 2005). Women with such pressure or dragging sensation might not have significant objective prolapse on examination.

Having excluded the time of the examination (objective POP tends to be more obvious later in the day), bladder and bowel fullness during the examination, as well as the patient position, a possible explanation for this discrepancy is the presence of an underlying central sensitivity syndrome. As mentioned previously CSSs includes conditions such as fibromyalgia, IBS, temporomandibular joint disease (TMJ), chronic fatigue

syndrome, tension headache/ migraines, restless leg syndrome, multiple chemical sensitivities, interstitial cystitis, myofascial pain syndrome and post-traumatic stress disorder (PTSD). As discussed earlier in the thesis, research studies have demonstrated that the patients suffering from this syndrome have higher symptom bother from their prolapse than those without (Adams K et al., 2014). Likewise, surgical intervention can be less effective for the relief of pain as seen following decompression in shoulder impingement syndrome (Gwilym SE et al., 2011).

It is currently unclear whether women who complain of a disproportionate dragging sensation to the objective pelvic organ prolapse or who have evidence of CSS benefit as much from POP surgery compared with women with no evidence of CSS. There are no published studies to date to answer this question.

The aim of our study was to compare the outcomes of pelvic organ prolapse surgery between women with evidence of CSS and women without evidence of CSS.

5.2. Method

This was a multicentre prospective cohort study. The study was approved by the West of Scotland Research Ethics Committee(13/WS/0319).

Using the PICO format:

Patients: Women scheduled for pelvic organ prolapse surgery (as agreed by patient and surgeon)

Inclusion criteria: Women scheduled for POP surgery who were willing to participate, could give informed consent and be able and willing to comply with all study requirements.

Exclusion criteria:

- Women who could not give informed consent.
- Women who had concomitant urinary or faecal incontinence surgery.

- Who had previous prolapse surgery in the same vaginal compartment.
- Women with severe vaginal pain were excluded from the study.

Intervention: Surgical treatment for pelvic organ prolapse. Outpatient/ Telephone follow-up was used to assess subjective and objective outcomes of surgery using internationally recommended outcome measures.

Comparison: Women without central sensitivity syndrome.

Outcomes: Both subjective and objective outcomes were compared using internationally recommended outcome measures as per the International Urogynaecological Association/ International Continence Society (IUGA/ICS) POP outcomes (Toozs-Hobson P et al., 2012).

The primary outcome was the prolapse symptomology using the validated Pelvic Organ Prolapse Symptom Scale (POP-SS) between the two groups at 3 months after surgery.

The secondary outcomes were:

1. Patient global impression of improvement-(PGI-I)
2. Prolapse stage at original site by POPQ
3. Subjective pain experience by using Short-form McGill's pain Questionnaire for somatic pain
4. Satisfaction with surgery by using the acronym EGGS (E- Expectations, G-goal setting, G-goal achievement, S-satisfaction between the two groups).

The following study questionnaires and forms were used in the study:

1. Central sensitisation inventory (CSI) – See pg-30 for description of the scale
2. PGI-I –This has been validated and consists of a single item that asks the participant to rate improvement of their condition using a seven-point scale with the following anchors: very much better, much better, a little bit better, no

change, a little bit worse, much worse, very much worse. Participants are considered to have had a positive outcome if they respond that they are "very much better" or "much better" (Yalcin I et al., 2003; Srikrishna S et al., 2010). This is a commonly used global index to rate the response to the treatment and is now frequently used in outcome studies. It is simple, direct and easy to scale.

3. POP-SS – This consists of seven items, each with a 5-point Likert response set (0 = never, 1 = occasionally, 2 = sometimes, 3 = most of the time and 4 = all the time). Total score ranges from 0-28. The question format and response set were modelled to standardise outcome measures in pelvic floor dysfunction research and clinical practice (Hagen S et al., 2009). This questionnaire was used as it is simple, brief and has been found acceptable to women. This is now been frequently used in research and clinical arena. This is also found to be very sensitive to detect a change in pelvic organ prolapse symptom score following conservative or surgical intervention (Hagen S et al., 2009).
4. Short form McGill's pain questionnaire (SF-MPQ)– There are three different parts to assess pain experience. The main component of the SF-MPQ consists of 15 descriptors (11 sensory; 4 affective) which are rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe. Three pain scores are derived from the sum of the intensity rank values of the words chosen for sensory, affective and total descriptors. The maximum score is 45 (33 on somatic subscale). There is no cut off for a clinically significant value, but higher scores indicates worse somatic pain. The other two parts are: The Present Pain Intensity (PPI) index of the standard MPQ (range from 0-5) and a visual analogue scale (VAS) ranging from 0-10 (Melzack R 1987). Although, the questionnaire was designed for the descriptive purpose, a mean improvement of >5 on total

scores (0-45) demonstrated a significant clinical change in patients with musculoskeletal conditions after rehabilitation and surgical intervention (Strand LI et al., 2008).

5. EGGS –The acronym EGGS was used to improve clinician understanding of the surgical outcomes. These are: E- expectations, G-goal setting, G-goal achievement, S-satisfaction using a visual analogue scale. (Brubaker L et al., 2005). This was used in the study because patient selected goals are now increasingly used to assess the improvement in the symptoms following any intervention. This has also been used widely in urogynaecology arena as an outcome assessment tool (e.g. following pessary use, pelvic floor muscle training, anti- muscarinic therapy for overactive bladder).

Women undergoing pelvic organ prolapse surgery were recruited and asked to complete these questionnaires and forms pre-operatively and 3-6 months after the surgery. The CSI was used to screen patients with symptoms suggestive of CSS and not as a treatment outcome measure.

The objective assessment of prolapse was undertaken using the pelvic organ quantification system (POPQ) (Bump RC et al.,1996) (see pg. 36) by vaginal examination to assess the stage of prolapse pre-operatively and at follow up.

The prolapse surgery was conducted with the surgeons being blinded to the patient's status of central sensitisation. Data on basic demographics including age, parity and BMI were also collected.

A successful outcome of surgery was defined as:

1) If there was a minimal improvement of 6 points in POP-SS score for the ques A1-A4 (the minimally important difference (MID) for the POP-SS).

2) Symptom rating as "very much better" or "much better" on the PGI-I scale.

3) Patient expectations met, and goals achieved and satisfaction with the outcome of their surgery using the 'EGGS' instrument.

4) Improvement in subjective pain experience as measured by McGill's pain instrument.

5) Improvement in the POP-Q stage. The objective prolapse is said to be persistent if the prolapse is up to or beyond hymen during maximum Valsalva manoeuvre. The definitions equate with those used in a previous large epidemiologic study looking at the prevalence and trends of pelvic organ prolapse (i.e. each POP-Q point greater than -1 cm) (Wu JM et al., 2014).

Women with evidence of CSS were designated as group 1 and women without evidence of CSS were named as group 2

Sample size: Hagen et al., 2008 reported that the POP-SS scale, which is scaled from 0-28 is likely to be skewed, therefore for the evaluation of suitable sample size to adequately power the study we used non-parametric tests. Again, from Hagen's data, the type of differences in scores may be 6 points on the scale, with two group average points being 9 and 3. We did not have any good estimates for the variance so choosing a conservative value equal to the difference (6 points) using a Mann-Whitney rank sum test we would need at least 20 per group for a power of 80% at a 0.05 significance level (two-sided).

Statistical analysis was performed using SPSS VERSION 25. Chi Square test and Mann Whitney U tests were used to compare the data. Statistic calculation was undertaken by the author and counterchecked by the statistician.

5.3. Results

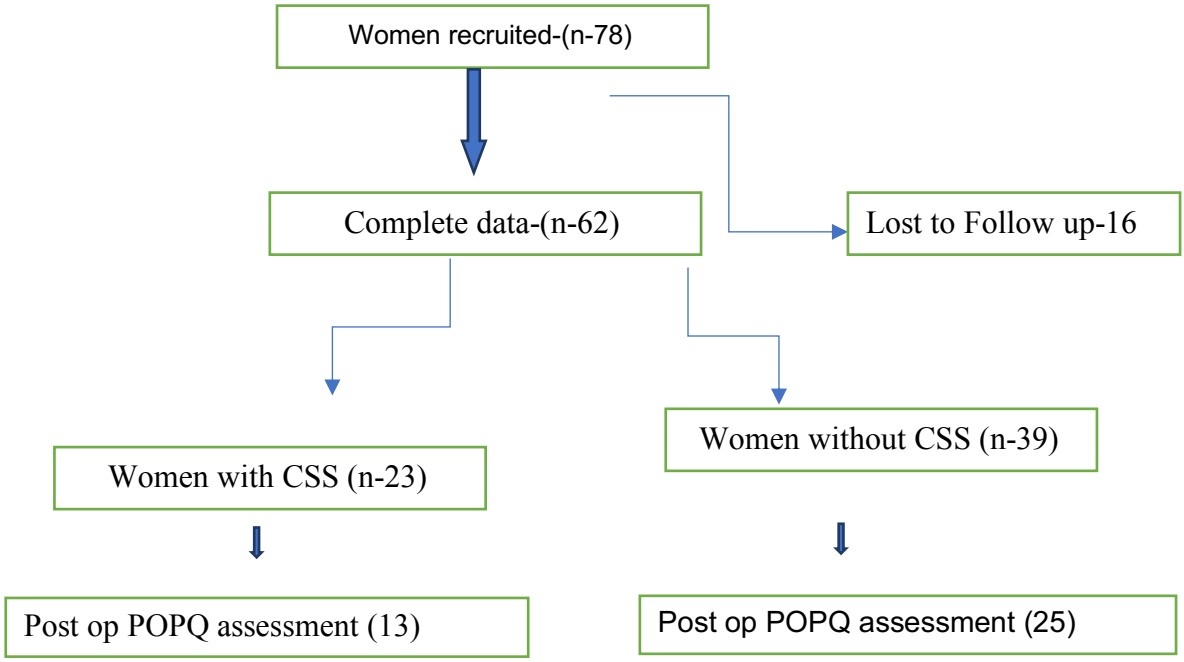

Figure 7: Central sensitivity syndrome Results

78 women were recruited. Complete data were available in 62 patients. Out of these 62 patients, 23 patients had evidence of CSS and 39 patients were without evidence of CSS.

There were few repeat POPQ assessments as some patients within the study declined vaginal examination (4 patients declined in group 1 and 6 in group 2) Some patients had telephone follow up consultations (6 in group 1 and 8 in group 2) because they did not attend outpatient clinics.

The mean BMI was 28.9 in group 1 and,26.7 in group 2 with mean Parity of 2 (table 10). The mean age was 60 yrs. in group 1 and 63.3 yrs. in group 2 (table 10).

A cut off CSI score of 40 was used to identify women with evidence of CSS as demonstrated by Neblett R et al (See chapter 3). The mean CSI score in group 1 was 53.13 (std dev (SD)11.90). The mean CSI score in group 2 was 21.23 (SD 9.76) (table 23)..

Two sample Kruskal Wallis test was used to compare the distribution of CSI scores, demonstrate that both groups followed a different distribution($p<0.0005$) .

Table 23: Showing demographics and CSI scores in both groups.

Demographics (mean value)	Women with CSS	Women without CSS
BMI	28.9	26.7
AGE (years)	60	63.3
PARITY	2	2
Mean CSI score (+/- SD)	53.13(+/-11.90)	21.23(+/-9.76)

Mean stage of prolapse in group 1 before surgery was stage II for anterior compartment (mean POP-Q system point Ba, 0 +/- 1.41, stage II for posterior compartment (system point Bp, 0.3 +/- 0.7) and stage I for apical, uterine (mean point C, -2.60 +/- 2.7). None of the patients had previous repair or hysterectomy.

In group 2 the mean stage of prolapse for anterior compartment was stage III (mean POP-Q system point Ba, 1.5 +/-2.56), for posterior compartment stage II (mean system point Bp-.1+/- 1.64) and stage II for apical compartment (mean system point C, -1.05 +/- 2.85). In this group,4 patients had a previous abdominal hysterectomy and 2 had a previous prolapse repair in a different compartment.

POP-SS score

Regarding the primary outcome of prolapse symptomology, women with evidence of CSS had higher pre- and post-operative POPSS scores compared with women without CSS. This was statistically significant (tables 24 & 25). The study also demonstrated that women with evidence of CSS (Group 1) had higher bother with their symptoms with less objective prolapse compared with women with no evidence of CSS (table 26) ($p<0.0005$).

Table 24: Showing pre-operative POPSS scores in both groups.

Groups	Mean	Range	Std Dev	Mann Whitney u test
Group 1-Women with CSS (N-23)	18.08	16.00	4.53	P< 0.0005
Group 2-Women without CSS(N-39)	12.35	20.00	4.74	

Table 25: Showing postoperative POPSS scores for both groups.

Groups	Mean	Range	Std dev	Mann Whitney u test
Women with CSS (N-23)	5.69	26.00	6.90	P=0.004
Women without CSS(N-39)	1.71	11.00	2.35	

Table 26: Showing preoperative POPSS scores with POP-Q system point quantification for both groups.

Groups	Mean pre-operative POPSS score	Mean system point Ba on POP-Q	Mean system point Bp on POP-Q	Mean system point C
Women with CSS (Group1)	18.08	0 +/- 1.41	0.3 +/- 0.7	-2.60 +/- 2.7
Women with no evidence of CSS (Group 2)	12.35	1.5 +/-2.56	1+/- 1.64	-1.05 +/- 2.85

Seventeen (73.9%) women in group 1 demonstrated improvement of minimum 6 points on POP-SS scale (a1-a4) whereas 38(97.4%) women showed improvement in group 2. This was not statistically significant (p=0.15).

McGill's pain score-

Although both groups had improvement in McGill's pain score following surgery, pain scores were higher in group1 than group 2 both pre and post- surgery (table 27,28).

In women with CSS (Group 1), the mean pre and post-operative VAS (for pain) on SF-MPQ was 3.91 and 1.60 respectively and the mean pre and post-operative PPI index was 1.69 and 0.91 respectively compared with women without CSS (group 2) where pre and post-operative VAS was 1.84 and 0.71 and the pre and post-operative PPI index was 0.12 and 0.10 respectively.

Table 27: Showing preoperative McGill'S pain scores in both groups.

Groups	Mean	Range	Std Dev	Mann Whitney U test
Women with CSS	16.17	32.00	9.69	P<0.0005
Women without CSS	6.48	25.00	7.58	

Table 28: Post-operative McGill's Score in both groups.

Groups	Mean	Range	Std Dev	Mann Whitney U test
Women with CSS	4.82	26.00	6.91	P<0.0005
Women without CSS	0.84	14.00	2.5	

EGGS

Ninety-five per cent (37/39) of women in group 2 were much or very much satisfied with the surgery with an average satisfaction score on VAS of 8.2, while only 69.5% (16/23) were satisfied with the outcome of the surgery in group 1 (p-0.005) (table 29). The average satisfaction score in this group was 6.2. The expectations and goals of both groups are shown in tables 30 and 31.

Table 29: Showing Satisfaction in both groups on VAS.

Groups	Patient satisfied	Patient not satisfied	
With CSS (Group-1)	16 (69.5%)	7 (30.5%)	P<0.005
Without CSS (Group-2)	37 (95%)	2 (5%)	

Table 30: Showing expectations and Goals of women with CSS.

Expectations (23)	Goals (23)
No bulge (14) 60.8%	Be comfortable, walk comfortably and return to normal (8)
More comfortable (3) 13.3%	Relief from periods (2)
Dragging sensation to go (2) 8.6%	Sex without pain (1)
Open bowels effectively (4) 17.3%	Not to use pessary (1)
	Open bowels easier (6)
	Not to digitate (4)
	No bleeding (1)

Out of 14 women whose expectation was to feel no bulge,13 achieved those goals. Out of 3 women whose expectation was to become comfortable and have no pain only 1 achieved this goal. Only 1 of the 4 women whose expectation was to 'open their bowel' more effectively, achieved this goal. There was no difference in the mean POP-SS score between women whose predominant expectation was to get rid of the bulge vs to be comfortable vs to open bowel effectively (17.85 vs 17.33 vs 16.5).

Table 31: Showing expectations and Goals of women without CSS.

Expectation (39)	Goals (39)
No bulge (31) 79.4 %	Comfortable-(20)
Dragging sensation to go (6) 15.4 %	Walk comfortable (5)
Bowel function to improve (1) 2.6%	Return to normal life (4)
Bladder function to improve (1) 2.6%	Able to go to the gym- more active (2)
	No pessary (1)
	No recurrent UTI (1)
	Pain free (1)
	Relief in heavy periods (1)
	Normal toilet (n-2)
	No dragging sensation (2)

In group 2 (women without CSS), only 2 did not achieve their goals. One was in the cohort with the expectation of no bulge and due to worsened bladder function, and the other who had the expectation of improving bowel function which did not happen following surgery. There was no much difference in the mean pre-operative POP-SS score

in this group between women whose expectation was no bulge (12.03) vs whose expectation was to have no dragging sensation (13) vs whose expectation was to improve bladder /bowel function (11).

PGI-I

Seventeen (73.9%) reported their symptoms to be very much better or much better on the PGI-I scale in group 1 compared with 97.4% women in group 2 (table 32) ($p< 0.0005$).

Table 32: Showing PGII scale in both groups.

PGII scale	Women with CSS	Women without CSS	Chi square test
1-2 (very much better, much better)	17(73.9%)	38(97.4%)	P<0.0005
3-6 (little better, no change, worse, very much worse	6(26.1%)	1(2.6%)	

POP-Q

In terms of persistence of objective prolapse (i.e. if the prolapse was up to or beyond the hymen during maximum Valsalva manoeuvre), 2/13(15%) women in group-1 had objective persistence of prolapse compared with 2/25(8%) in group 2. ($p<0.0005$) (table 33,34).

Table 33: Showing persistence of objective prolapse in both groups.

Persistence of Objective pro-lapse	Women with CSS	Women without CSS	Chi square test
Persistent pro-lapse	2(15%)	2(8%)	P<0.0005
No prolapse	11(85%)	23(92%)	

Table 34: Showing pre and post-operative POP-Q in group1.

GROUP-1 with CSS	POP-Q Before surgery			POP-Q after surgery (4-6-month FU)		
Pt no	Ba Leading edge an-teriorly	Bp-leading edge poste-riorly	C	Ba Leading edge an-teriorly	Bp leading edge poste-riorly	C
1	-1	0	-1	-2	-2	-6
2	-1	1	-3	+2	-2	+2
3	0	-2	-5	-2	-2	-5
4	-3	0	-6	-2	-2	-6
5	-2	0	-5	-2	-2	-6
6	0	-2	0	-2	-1	-5
7	+2	+1	-1	0	-1	-6
8	0	2	-7	-3	-3	-7
9	2	-2	-1	-2	-2	-7
10	-3	0	-6	-2	-2	-5
11	-1	-2	+1	-3	-1	-4
12	-2	+3	-5	-2	-3	-5
13	+2	-1	-4	-2	-2	-5

Note-The above table (34) displayed the leading edge of prolapse as per International Continence Society, the stages of Pelvic organ Prolapse determined by POP-Q measurements are based on the most distal prolapse and is used in most researches (Ingrid N et al., 2004).

Multiple linear regression analysis was also conducted to see if the preoperative POP-SS, McGill's scores. patient perception of improvement (PGI-I), EGGS and Post-operative POP-SS, McGill's) is related to the severity of CSI scores treating CSI as continuous data. This revealed a non- significant model with moderate effect of CSI scores (Table 35). Individually, only pre-operative POP-SS scores approached a significant Beta of 0.682 (Table- 36). Inspection in the trend in the data suggest that there was no linear relationship of CSI scores with patient satisfaction and patient global impression of improvement. This may be due to the small numbers as multiple regression usually works well with large number

Table 35: Model summary of the Multiple Regression analysis.

R	R square	Adjusted R square	Std Error OF the estimate
.694	.482	.240	10.38223

Table 36: Showing coefficients of each predictors after multiple regression analysis.

	Unstandard-ized B	Coefficients Std Error	Standardised coefficients Beta	t	Sig
constant	-3.494	18.002		-.194	.849
PGII	-.718	1.772	-.085	-.405	.691
Preop McGill	.253	0.253	.206	1.001	.333
Preop POPss	**1.791**	**.601**	**.682**	**2.981**	**.009**
Post op MCGILL	1.121	.509	.652	2.203	.044
Post-op POPss	-.530	.771	-.307	-.686	.503
EGG	4.934	6.246	.186	.790	.442
Satisfaction score	2.035	1.365	.561	1.491	.157

5.4. Discussion

Our study has demonstrated that women with evidence of CSS have less successful outcomes from POP surgery in terms of patient satisfaction, goal achievement and persistence of pain are concerned. Although, there was no persistence of objective prolapse in 11/13 women (85%), the global impression of improvement was seen only in 74% in women with evidence of CSS, whereas in women without CSS, the global impression of improvement was seen in 97.4% women with no persistence of objective prolapse in 92% women (see tables 19,20). There was no linear relationship seen between CSI scores and patient global impression of improvement and satisfaction

These findings demonstrate that for patients in group 1 with CSS, the subjective outcome is less favourable than in patients in group 2. Jacob N et al demonstrated that patients with presurgical evidence of Fibromyalgia/FMS-like symptoms experienced a less significant improvement in pain and no improvement in somatic symptoms as opposed to patients without evidence of FMS. The latter group experienced significant improvement in both pain and other symptoms after surgery (Jacob NA et al., 2017). This is similar to the findings of our study where patients with evidence of underlying CSS have less satisfaction (based on Satisfaction part of EGGS) with the surgery and less improvement in their symptoms despite a clinically evaluated, good anatomical outcome.

As mentioned previously, Central Sensitisation is a concept developed over recent years to explain the manifestation of chronic pain in which there is no clear anatomical basis. The understanding of both CS and CSS is more than a semantic consideration and appears to carry important practical relevance. Patients can potentially be stratified according to the intensity or periodicity of the symptomology relating to the underlying CSS. This information might help tailor treatment modalities used to improve the

chance of a successful outcome from treatment. The management of women who are considered candidates for prolapse/POP surgery typically includes anatomical evaluation by vaginal examination/POPQ staging and the severity and effect of prolapse symptoms on women's quality of life. While these measures will be important in the process of surgical decision-making, the results of the current study imply that additional factors may be worthy of evaluation. e.g. presence of a CSS as this might lead to persistent symptoms despite anatomical correction.

Issues such as disturbed or unrefreshing sleep, symptoms of irritable bowel, difficulty with memory and concentration, the presence of widespread pain, previous diagnosis of fibromyalgia, CFS, TMJ, PTSD and depression, are all common features of CSSs and can be helpful in the assessment and diagnosis of CSS.

It also seems appropriate to include identification of myofascial trigger points during vaginal examination as a part of prolapse assessment. It is likely that that levator myalgia, which has previously been shown to be present in 24% of gynaecological patients presenting with pain might represent another manifestation of central sensitisation and might contribute significantly to chronic pain in women with pelvic floor dysfunction (Adams K et al., 2014). Treatment modalities may then be tailored accordingly.

Surgically induced neuropathic pain (SNPP) is seen around in 10-50% of patients after common surgical procedures such as groin hernia repair, breast and thoracic surgery (Kehlet H et al., 2006) while, severe SNPP has been observed in around 2-10% of patients (Kehlet H et al., 2006). The presence of pre-operative pain (Gerbershagen HJ et al., 2010), and the patient's psychological state (Hinrichs-Rocker A et al., 2009) can increase the risk of persistent SNPP. There is also evidence in the literature that baseline preoperative pain is a predictor of chronic postoperative pain after hysterectomy (Theunissen M et al., 2016). Similarly, a meta-analysis of patients undergoing total

knee arthroplasty found that pain at other sites, catastrophizing, and depression were found to be predictors of chronic postoperative pain (Lewis GN et al., 2015). Our study also demonstrates, unsurprisingly, that there is persistent higher somatic pain score in women with evidence of CSS. Borsook proposes that it is important to identify the predictors of persistent SNPP (such as patients with manifestations of CSSs) before any surgical treatment is undertaken (Borsook D et al., 2013).

Women with fibromyalgia (FM) were also found to report pelvic floor symptoms at a severity greater than women presenting to a urogynaecology practice without FM despite being the same age (Jones KD et al., 2015) and therefore, it is possible that enhanced sensory processing makes women with FM more aware of pelvic organ prolapse symptoms than women without FM. This was similar to the findings of our study above which demonstrated that CSI score and POP-SS scores have linear relationship.

FM is also found to be a risk factor for the development of pelvic pain after vaginal mesh implantation for treatment of pelvic organ prolapse (Elizabeth JG et al., 2017). This was not a procedure undertaken in our study. However, it might suggest that increased central sensitisation as part of a deteriorating CSS could be another reason for the sustained post-operative pain noted after mesh surgery in addition to any localised irritation from the mesh itself.

There is a large body of evidence that sensation can be enhanced through a variety of dysfunctional pain pathways (Julien N et al., 2005). This might explain why these patients are highly symptomatic.

Various treatment modalities have been used in an effort to desensitise the CNS in patients with CS. These include pharmacological (pain modulators), manual therapy (release of myofascial trigger points) and psychological stress management. Regarding the pharmacological approach – drugs will work primarily by (1) blocking the

peripheral drive which is maintaining the sensitisation or (2) interacting with the central transmitter systems involved in the facilitated gain (Arendt-Nielsen L et al., 2018). Examples of drugs which can have an inhibitory effect on temporal summation include dextromethorphan (Price DD et al.,1994), ketamine (Arendt-Nielsen L et al., 1995), imipramine (Enggaard TP et al., 2001), gabapentin (Arendt-Nielsen L et al., 2007), oxycodone (Suzan E et al., 2013), and venlafaxine (Yucel A et al., 2005). Serotonin-noradrenaline reuptake inhibitors (SNRI's), such as duloxetine, have a broad efficacy across a number of different chronic pain conditions, such as osteoarthritis, fibromyalgia and peripheral neuropathic pain (Lunn MP et al., 2014). SNRI's drugs activate noradrenergic descending pathways along with serotonergic pathways (Millan MJ, 2002). The a2-δ ligands centrally inhibit the release of neurotransmitters (e.g. noradrenaline, serotonin, substance P) and potentially reduce CS by decreasing descending pain facilitation (Donovan-Rodriguez T et al., 2006). Gabapentin and pregabalin are the two drugs that exert their effect by binding to the α2-δ subunit of calcium channels (Thorpe AJ et al., 2010). Pregabalin is found to be effective and remarkably safe and mitigates the symptoms of various types of neuropathic pain (Verma V et al., 2014).

Tapentadol is a centrally acting analgesic and the CPM enhancing effect is due to its dual action (μ-opioid receptor agonist plus a norepinephrine reuptake inhibitor) and has been observed with repeated dosing over weeks. This is found to be effective and well tolerated in various chronic pain conditions (Riemsma R. et al., 2011) such as OA pain (Steigerwald I et al., 2012b), low back pain (Buynak R et al., 2010), painful peripheral diabetic neuropathy (Schwartz S et al., 2015), and cancer pain (Kress HG et al., 2014). Non -pharmacologic strategies such as cognitive behavioural therapy and biofeedback can influence pain sensitisation in some patients e.g. A recent metanalysis has shown

mixed efficacy from CBT in pain management in patients with fibromyalgia. CBT was found to be better for reducing depression and increasing pain coping skills but was not found to be effective in improving pain and fatigue (Bernardy K et al., 2010). Electromyographic (SEMG) biofeedback has been found to be effective in improving pain. Babu et al demonstrated a significant reduction in VAS score for pain as well as a reduction in the tender points in patients with FM with the use of EMG biofeedback (Babu AS et al., 2007), however, Glombiewski et al reviewed seven different studies on biofeedback in patients with fibromyalgia. Biofeedback was found to be effective in reducing pain intensity, but the trials were of poor quality. There was no benefit on fatigue and sleep (Glombiewski JA et al., 2013). Taken this into consideration, biofeedback is not recommended by European League Against Rheumatism (EULAR) (Macfarlane GJ et al., 2016).

Some of the symptoms associated with POP such as back pain, vaginal pain, bowel and bladder dysfunction can be due to a non-relaxing pelvic floor, or presence of levator myalgia which may also be a manifestation of central sensitisation (Adams K et al., 2014). Physical therapies to alleviate hypertonicity can be undertaken in these women before surgery. For example, Thiele in his study of 324 patients with coccydynia reported improvement in 62% patients with massage only. He performed the massage by applying pressure along the fibres of pelvic floor muscle (according to the patient tolerability) about 10-15 times on each side of the pelvis during one session (Thiele GH 1963).

Strategies such as moderate aerobic exercise is an integral part of the treatment of patients with fibromyalgia. Recently, tai chi intervention was found to have greater benefit than aerobic exercises in terms of improvement of symptoms of fibromyalgia (Wang C et al., 2018). Tai chi is a multicomponent mind body intervention which

combines physical, spiritual, psychosocial and behavioural components to boost health and fitness. Wang C et al randomly assigned patients either to aerobic exercise (24 weeks, twice weekly) or to tai chi intervention (12-24 weeks, once or twice weekly). Patients were then followed for 52 weeks. Maximum improvement was seen at 24 weeks (Wang C et al., 2018).

Various other strategies have been described in the literature for non-relaxing pelvic floor such as injection of local anaesthetics on trigger points, acupuncture, biofeedback and neuromodulation. For example, Clemens et al reported an improvement with bio-feedback in chronic pelvic pain on visual analogue score reduction from 5/10 to 1/10 (Clemens JQ et al., 2000). Ger et al found good short- term relief with local injections but minimal long- term benefits (Ger GC et al., 1993). Short wave diathermy was used by Sinaki reporting good results in terms of symptom improvement (Sinaki M et al., 1977).

Professor Michael Hyland developed a body reprogramming guide for patients with central sensitivity syndrome. Body reprogramming is an approach to help recovery in these patients based on the theory of Hyland model. He compared the body with a computer that sometime can go wrong, and which can have software (consists of instructions sent to the whole body) and hardware (different parts of the body such as eyes, ears, lungs and heart) problems. The software is not visualised, but it directs the functioning of the hardware. The guide has 4 sections: The first section describes the theory. The second section gives information about what to do to promote recovery (such as stress reduction and avoidance, creative positive emotions, deep relaxation, optimal movement, medicines and eating). The third section helps with managing symptoms (such as pain, fatigue, sleep, IBS). The final section gives advice to put everything into practice (such as looking after yourself, finding a routine) (Hyland ME et al., 2016).

Although, a broader approach to desensitise the CNS could be adapted in these group of patients (Baert I et al., 2016) we raise the question of whether there is any role of these treatment modalities in improving the outcome of surgery in women with POP and CSSs? Further research is required to clarify this.

The strength of this study is that it is the first study to compare the outcomes of prolapse surgery between women with underlying CSS and women without CSS.

There are several limitations in this study : 1) Measurement of pain perception was undertaken with the help of SF-MPQ, which is a widely used instrument to measure characteristics of pain (sensory and affective), however its use for assessment of neuropathic pain diagnosis is limited as relevant descriptions for characteristics of neuropathic pain were not used in this version (Dworkin RH et al., 2009). 2) Central Sensitisation inventory(CSI) was used to identify women with CSS which is a validated questionnaire (see page 30) however, there was no quantitative sensory testing done to assess the severity of pain sensitisation. 3) The other limitation of this study is the small numbers with a relatively short period of follow-up. However, there were no previous studies to guide us on numbers and the power calculation was made based on POP-SS and not CSI scores. 4) Another limitation of the study was that few patients had a post-op POPQ, due to either to telephone follow up or refusal of some patients to be examined vaginally at the time of follow up. However, the primary outcome was as internationally recommended, a subjective/symptomatic one with POPQ being a secondary outcome and on regression analysis patients with higher CSI scores were found to have worse prolapse symptom scores. 5) There was no linear relationship of CSI scores seen with patient satisfaction and patient global impression of improvement. This may be due to the small numbers as multiple regression works well with large number 6) Around 21% patients lost to follow up. Along with this, information on POP-q was

available only in 61% patients. This is a potential of bias and may be leading to over-estimation of effect of CSS on pelvic organ prolapse surgery in terms of poor subjective outcomes

Therefore, it is important to note that the results of the current study should not be interpreted as recommending the avoidance of prolapse surgery in patients with CSS (as there was an improvement seen in 70% of women. Also, to note that one of the patients had recurrence of prolapse (although in another compartment). This has possibly led to the dissatisfaction of the surgery. Although, this skewed our results i.e. if we assume that this patient would be satisfied then improvement in CSS group will increase to 74% but still it is less when compared to those without CSS (95%)

Even with these limitations, the result suggest that careful considerations should be given to this group of women with a detailed understanding of their needs and evaluation of the severity of their global symptomology. Also, adding alternative treatment strategies before considering surgery might be appropriate in many to reduce the degree of sensitisation. Full discussion at counselling and robust informed consent regarding the risk of persisting symptoms should be undertaken with the patient actively involved in the decision-making process.

The study highlights the need to find strategies to best manage women with POP and CSS. For example, should physiotherapy be offered in all stage 1 and 2 POP in this group of women or a trial of the vaginal pessary to assess its effect on symptoms? Surgery would then only be undertaken if symptoms are improved or a trial of desensitising pharmacotherapy or other non-pharmacological options given if they are not. Further research is required to answer these questions.

The results of this study suggest that screening women for CSS before POP surgery especially where there is a difference between symptoms and the degree of prolapse on

an objective assessment might facilitate potential management. This would include better counsel and informed consent.

5.5. Conclusion

Our study has demonstrated less favourable outcome of surgery for POP in women with CSS within our patient cohort, especially in terms of persistence of symptoms including dragging sensation and overall patient goal achievement and satisfaction.

The main expectation of women in both groups was to become comfortable, however, only 70% of women in group 1 felt their goals were met and were satisfied compared with 95% of women in group 2. These results are similar to study by Blcan and his team where they found that patients with FM had less satisfaction despite of improvement comparable to the controls. (BIcan O et al 2011). This should enable us to counsel women for realistic expectations especially where there is evidence of underlying CSS and optimise the shared decision-making process.

Additional research is indicated in order to evaluate the interaction between CSS and surgical interventions, the interaction between CSS and treatment interventions targeting CS and the impact on the symptoms of pelvic organ prolapse.

Recommendations for future research-

1. Further research is advised with large numbers (to calculate sample size) based on our regression model to assess the relationship of the CSI scores with patient satisfaction and with long term follow up (With a medium effect size (f' = .15), a power of 80%, and a $p < .05$ criterion, we will need 103 participants in each group).

2. Role of Pain catastrophising on the outcome of pelvic organ prolapse surgery

3. The results of our work have enabled us to pilot another study in assessing the outcome of mesh excision surgery undertaken at Singleton Hospital, Swansea. On basis of this, our unit is currently practicing more conservative approach and aggressive pain

management programme in patients with CSI score of over 40 compare to those who have CSI score less than 40.

4. Another protocol for a randomised trial to compare the effect of physiotherapy vs physiotherapy and psychology on symptoms of POP in patients with CSS is also ready for future research. This will help us to find evidence on best management strategy in this cohort of patients. This will be undertaken with co authorship of clinical psychologist and physiotherapist

The protocol is as follows:

Aims

The research aims to assess the impact of psychological support on outcomes for treatment of patients with pelvic organ prolapse (POP) who have symptoms suggestive of central sensitivity syndrome (CSS). It will: (i) compare the benefits of combined PFMT and psychotherapy with PFMT alone in women with POP and evidence of CSS; and (ii) establish whether expectations of treatment efficacy prior to treatment impact on outcomes and can be modified by psychological support.

Background

Pelvic organ prolapse (POP) is defined as the descent of one or more of the following: anterior vaginal wall, posterior vaginal wall, apex of the vagina (cervix to uterus), or vault (cuff) after hysterectomy. POP affects almost half of all women over 50 years of age, with a lifetime prevalence of 30% to 50%. Women with a normal life expectancy will have an 11% to 12% chance of undergoing at least one operation for prolapse, with a re-operation rate of 29% by the age of 79 years. The principal symptom manifested in prolapse is the perception of a bulge within the vagina. A significant proportion of women, however, complain of a dragging sensation without a physically confirmed bulge on examination, but these women may still proceed to prolapse surgery. It is

known that anomalies exist between the pathology (i.e. prolapse) and degree of dragging sensation, and there is on-going debate regarding the most appropriate management for this cohort of patients.

One increasingly popular explanation for this discrepancy between the 'dragging' perception and degree of prolapse is related to variability in the processing of sensory stimuli. The mechanism suggested involves the augmentation of pain transmission, secondary to a process known as Central Sensitisation (CS). Central Sensitisation is a pathological process that affects the central nervous system, leading to reduced pain threshold, and an altered sensation of a normally non- painful stimulus. There is an exaggerated pain response (hyperalgesia) – an extension of the response and pain sensation to normal touch and pressure (allodynia).

This condition has been proposed as root aetiology for several conditions, such as-Fibromyalgia, Chronic Fatigue Syndrome, Temporo-mandibular Joint Disorders, and Complex Regional Pain Syndrome, which are collectively termed as Central Sensitisation Syndrome (CSS). The patients suffering from this syndrome have higher symptom bother, due to underlying central sensitisation. Furthermore, CSS can result in considerable psychosocial impairment, work disability, and increased utilisation of health care resources by patients. Despite increased understanding of the mechanisms involved in CS pain, its treatment remains a challenging issue.

Pelvic Floor Muscle Training (PFMT) is the mainstay of conservative management of POP. The purpose of conservative treatment is the reduction of symptoms, the prevention of worsening POP, increased support of the pelvic floor musculature, and avoiding or delaying surgery. However, PFMT may not be that successful for women who present evidence of CS. Certainly, studies have shown that women undergoing PFMT for

a variety of pelvic floor dysfunctions (including POP) fare less well with this treatment if they also exhibit psychological problems, such as those involved with CSS.

Our hypothesis is that women with POP and evidence of CS will have better outcomes with a combination of PFMT and psychological support than with PFMT alone. This view is based on a similar study showing the advantage of such a combination treatment for women with pelvic floor dysfunction and mild psychological problems. This latter study noted that brief psychological support offered to these women increased patient co-production, involving improved attendance and treatment outcomes. A similar finding from the current sample would allow roll-out of such psychological support to women with POP and CSS, and the improved treatment outcomes would have the potential to offer substantial cost-savings in terms of avoidance or delay of surgery, improved co-production, and enhanced patient experience of treatment.

Participants and Recruitment

Consecutive women patients referred for PFMT treatment in the physiotherapy department for Grade 2 POP will be asked if they would like to participate in this study. To allow sufficient time to consider participating in the study, all women will receive a patient information sheet regarding the study along with their appointment letter. This information sheet will make clear that their treatment will not depend on their participation in the study. On arrival at their initial appointment, women will be given the chance to discuss their participation with the treatment team, and will give their consent by completing and signing a Consent Form, after they have had time to think about their participation and ask any questions that they may have.

Inclusion Criteria

- Participants willing and able to give informed consent for participation in the study.

- Females aged 18 years or above.
- Participants able and willing to comply with all study requirements.
- Women with Grade 2 pelvic organ prolapse (as they are more likely to comply with PFMT).
- Women with evidence of CSS.

Exclusion Criteria

- Females under the age of 18 years.
- Women who are unable to give informed consent.
- Women with Grade 3/4 POP (who are more inclined towards a pessary or surgery).

Design and Methodology

Following their consent, the patients will be asked to complete a battery of assessment questionnaires (taking about 15min in total). The Central Sensitisation Inventory (CSI) score will be used to identify women with evidence of CSS. Women with evidence of CSS will then be randomised for PFMT alone or for PFMT with psychological support. The randomisation will be performed by a random number generator.

All patients will then experience their PFMT treatment as usual, which will entail one group session each month over four/five months, along with two individual appointments at the start and end of the PFMT treatment. In addition, the experimental group will receive psychological motivational support in addition to their medical treatment based on that previously shown to be effective in supporting women with pelvic floor dysfunction undergoing PFMT. This will entail a 20min group-based session focusing on motivation and health values after the 2nd, 3rd, and 4th PFMT sessions.

After the last session of treatment, the patients will complete the same battery of tests. The changes across the objectively- and subjectively reported health status and in the patient-reported outcomes will be measured. Additionally, the relationship between the baseline patient-reported expectation of improvement and the objective (physical measures), and subjectively reported (general health and quality of life) outcomes, will be assessed.

The difference in the change in levels of functioning in the primary and secondary outcome variables in the two groups will be assessed using independent groups t-tests. Based on adopting a $p < 0.05$ rejection criterion, 80% power, and a medium-sized effect $d = 0.5$ (Osborne et al., 2016, indicates a large effect size, but an assumption of a medium-sized effect will be more conservative), then 102 participants (51 per group) will be needed for a one-tailed hypothesis. On the assumption of a large effect size, $d = 0.70$, this would be 52 participants (26 per group). It has been estimated that between 30% to 40% of patients display CSS , and given that upwards of 200 patients per year are referred to Women's Health at Singleton Hospital for PFMT, the estimated numbers above should be achievable. These numbers will also allow sufficiently powered correlational analysis between predictor outcomes and improvements to be conducted.

Outcome Measures

Primary Outcome

Pelvic Organ Prolapse Symptom Scale (POP-SS,) is a patient-reported outcome, measured by 7 questions relating to the number and frequency of prolapse symptoms, each with a 5-point Likert scale (0 = never to 4 = all of the time). A total score range of 0 to 28 is calculated by summing the seven questions to derive the POP-SS score. The question format and response set were modelled to standardise outcome measures in

pelvic floor dysfunction research and clinical practice. Internal reliability (Cronbach α) ranges from 0.72 to 0.83.

Secondary Outcomes

Euro-qual 5D (EQ-5D) is a quality of life (QoL) instrument in which patients describe and value their health on five domains (mobility, self-care, pain, usual activities, and psychological status), and rate their general health on a visual analogue scale of 1-100. It has been extensively validated and its reliability proven.

Patient Global Impression of Improvement (PGI-I) has a single item relating to how much the patients' perceive their condition to have improved, scored 1 ("very much improved") to 7 ("very much worse"). This tool has been validated, and participants are considered "successfully" treated if they respond that they are "very much better" or "much better".

McGill's Short Pain Questionnaire (MSPQ,) measures pain through 15 descriptors (11 sensory; 4 affective) which are rated on an intensity scale (0 = "none" to 3 = "severe"). The scale has good test-retest reliability.

Questionnaires

Central Sensitisation Inventory (CSI;) is a published and validated questionnaire, assessing 25 health-related symptoms commonly noted in CSS, such as: "I feel unrefreshed when I wake up in the morning" or "I am sensitive to bright lights". These questions are scored on a scale of 0-4 (0 = "never" to 4 = "always") giving a score from 0 to 100. It is suggested that a cut off score of 40 indicates the presence of central sensitisation.

Stanford Expectations of Treatment Scale (SETS,) measures patients' positive and negative treatment outcome expectancies through six items, each scored on 7-point

scale (“strongly disagree” to “strongly agree”). It produces two subscales: positive expectancy (Cronbach $\alpha = 0.81–0.88$) and negative expectancy (Cronbach $\alpha = 0.81–0.86$).

Chapter 6 - A qualitative study of women's experiences of prolapse surgery in those with evidence of central sensitivity syndrome

6.1. Introduction

It is well known that there are better results from a treatment when patients are involved in their care. Surgeons often presuppose the outcome of the surgery which may not be the same for the patients. The document "No decisions about me without me" demonstrated that the concept of concordance should be applied to achieve the greatest outcome from a treatment (Snowden A et al., 2013) and therefore, there is an increasing trend to include outcome measures based on patient's expectations (Toozs-Hobson P et al., 2012).

Patient reported outcome measures can be affected by several factors such as previous personal experience, those of friends and relatives, patient expectation and understanding of the condition, mental/psychological state and attitude of the clinician. These factors can impact on the understanding of the concept of cure or successful outcome in surgery.

Achieving normal restoration of anatomy might be the aim of the surgeon but, not necessarily of the patient. Cure is difficult to define in this context e.g. the patient might be cured of their presenting complaint anatomically but that would not necessarily mean a successful outcome if there is development of new symptoms or complications e.g. in the case of POP surgery: bowel, bladder or sexual dysfunction (Srikrishna S et al., 2008).

Several qualitative studies have been undertaken to understand women's preference of treatment such as for pelvic organ prolapse (Basu M et al 2011), their perception of risk reduction (Brain K et al., 2004), exploring patient experiences both pre and post-operatively to produce positive outcome following treatment (De Graenreid-Yates Sacha L 2015).

For example, Brain and her colleagues (Brain K et al., 2004) found limited understanding of the concept of prophylactic oophorectomy in the prevention of ovarian cancer while Sacha L in 2015 demonstrated the importance of education and understanding of the patient's needs in order to have an effective partnership with healthcare providers. He also discovered the need for patients to be cared for as individuals, with consideration for their whole life experience during the entirety of surgical care.

The understanding of patient's needs, and expectation enables patients to be involved in decision making for the proposed treatment and this might potentially enhance outcome where provider and recipient have mirrored expectations.

It has been previously demonstrated in a prospective cohort study (see chapter 4) that there is poor subjective benefit following prolapse surgery in women with central sensitivity syndrome. The current qualitative study was, therefore, undertaken to understand patient's experiences, individual needs, expectations and views on the reasons for the poorer outcome of surgery i.e. in those with central sensitivity syndrome (CSS). This might help us to identify areas of where improvement in management can result in better outcomes.

To facilitate this aim, we interviewed women with poor outcomes in CSS group of the above prospective cohort study (see chapter 4). Poor outcomes were defined on the basis of persistence of symptoms and suboptimal responses on the patient global impression of improvement scale (see chapter 4).

6.2. Method

A qualitative study, using semi-structured interviews with women with Central Sensitivity Syndrome, who had subjectively poor outcome following pelvic organ prolapse surgery was conducted in the month of July 2018. The research investigation was endorsed by the Scotland Research Ethics Committee.

The women previously described in chapter 5 were followed at 4-6 months post-surgery. Those with poor outcomes based on the persistence of symptoms and the patient global impression of improvement scale (PGI-I) were identified. Having confirmed that formal consent had been documented during the original trial, semi-structured interviews were scheduled. The opportunity was provided for further questions during the telephone confirmation of the initial consent.

The structure of interview -The interview contained set of predetermined questions. There were 5 open and 2 closed ended questions. The open-ended questions were used. This allowed us to capture independent thoughts of each patient with CSS who had poor outcome with the surgery. All the questions were designed to capture the journey of these patients from symptom diagnosis to surgical treatment in order to understand their expectation and satisfaction

The two closed ended questions – "Do you feel that persistence of your symptoms is something to do with your nerves?" "Have you ever heard about central sensitisation or central sensitivity syndromes" were used keeping in mind the objective of our study to assess the awareness of CSS among the patients

The wordings of the interview questions were developed with the help of a psychologist. The questions were tested within the department with non- clinical staff (cleaners, secretaries, and receptionist) before the patients were interviewed.

Interviews were then conducted by two independent researchers who had not been involved in that patient's care (psychologist and author). All interviews were conducted in a private room within the hospital and university (Swansea). Demographics data and details of surgical interventions were recorded in a standard proforma prior to interview. Interviews lasted from 15 -25 minutes (Mean length: 17.8 minutes) and were tape-recorded.

All recordings were anonymised and transcribed using Trint software by the author.

6.3. Analysis

A thematic approach-based framework was utilised for the analysis based on that previously described by Marshall & Rossman (Marshall C et al1999).

Thematic analysis is a generic approach to data analysis and is widely used in qualitative research. It enables data sources to be analysed in terms of the principal concepts or themes and to enable the data to be reduced to key ideas.

The structure of the analysis used for the whole interview in this study is shown below:

1. Organization and familiarization with the data. Interviews were listened to and transcripts read and re-read by 2 investigators to familiarize themselves with their content.

2. Identification of categories and themes which reflected and addressed the core research questions.

3.Interviews were listed and coded according to these categories.

4. Interviews were summarised using the QSR NVivo 8 Computer-Assisted Qualitative Data Analysis Software.

5. Once the coding system is completed, the primary themes are identified and summarised to determine the conclusions.

6.4. Results

A total of 23 women with evidence of CSS had POP surgery during the prospective cohort study. Out of 23, 7(30%) had poor subjective outcomes in terms of patient global impression of improvement, goals achievement and satisfaction, 1 patient had achieved their goals partially. These 7 women with poor outcome were approached. Five women replied and agreed to the interview. The demographics, detail of surgery, CSI scores patient global impression of improvement scores, POPSS scores, McGill's score, POP-

Q, expectation and goals of these women are shown in tables 37 and 38. All the questionnaires used have been explained in chapter 5.

Table 37: Demographics, type of surgery, PGII, POP-SS scores, McGill's pain scores in this group of women.

Patient no	BMI	Parity	Type of surgery	PGII	POPSS scores		McGill's Pain score		CSI scores
					Before surgery	After surgery	Before surgery	After Surgery	
1	32	P3	Post repair	6	24	20	12	12	49
2	25	P3	Posterior repair	2	18	10	1	1	52
3	25	P3	Post repair	3	14	7	13	6	44
4	38	P1	Post repair	5	22	26	21	18	66
5	31	P2	Vag hyst, a&p repair	3	14	8	25	26	58

Table 38: Showing expectation, goals, satisfaction and POP-Q scores in this group of women.

PATIENT	Expectation From surgery	Goals achieved	Satisfaction From surgery	POP-Q (before surgery)	POP-Q (after surgery)
1	Opens bowel effectively	Not met	Not satisfied	Grade 2 rectocele	Tel FU No examination
2	Improve Bowel	Partially met	Not satisfied	aa-2, ap-0, bp-0, c-5	aa-2, ap-2, bp-2, c-5
3	Easier to open bowel, not feel bulge	Not met Still digitate Sex painful	Not satisfied	aa-3, ap-0, c-6	aa-2, ap-2, c-5, ap-2, bp-2
4	Improves dragging sensation	Not met	Not satisfied	aa-1, ap+1, c-3	Aa+2, c+2, ap-2 (improved compartment of surgery)

5	Not to feel prolapse	Not met Persistent dragging sensation	Not satis-fied	Aa+2, c-1, ap-0	Aa-0, c-6, ap-1

Four categories were identified.

1. Understanding

Women's understanding of their symptoms and their relationship with prolapse was poor. The majority sought help due to their bowel, bladder problems rather than feeling of bulge/prolapse; in fact, only one patient had the symptom of dragging sensation. They were made aware of prolapse only during the clinic appointment for bowel or bladder symptoms, following an examination by their clinician. Typical examples include:

"Initially I went to doctors for haemorrhoids and during smear test, they told me I had a prolapse." (patient 2)

"I saw the GP due to feeling of urgency to urinate, burning sensation when I would urinate, and it was getting worse and not manageable. My first thoughts were that I was suffering from cystitis." (patient 4)

"Below were very uncomfortable with leakage of stuff coming down with often pains in the lower back." (patient 5)

"I got a lot of diarrhoea, I had difficulty in emptying the bowel properly, it was very uncomfortable. I had to put my hand up and press my perineum to empty my bowels and, in the end, I had to do irrigation which was not fun." (patient 1)

Some women expanded on this theme with comments that shows their worries and concerns rather than them being bothered with the symptoms.

"I understood if this is prolapse, then that can get worse and can actually become external and that's something I did not want." (patient 2)

"My concern was the worsening of urinary leakage and worsening of back pain "(patient 5)

"I think everybody in their mind think cancer." (patient 2)

"I was concerned of it getting worse and with old age more likely to have lots of problems." (patient 3)

2. Expectations

All Women were hoping to have normal bladder, bowel, sexual function along with complete resolutions of discomfort and back pain except one

"I would be able to function normally, not have problems in opening bowels, able to have normal sex." (patient 1)

"I expected it really improve my bowel control." (patient 3)

"I hoped it would all go away- the discomfort, back pain, pain on passing urine and urgency." (patient 5)

"I have little expectation other than to prevent the problem getting worse" (patient 4)

3. Reasons for failure

None of the women felt that there was any relevance between persistence of their symptoms or poor outcome and the presence of an underlying central sensitivity syndrome. They all felt that persistence of symptoms were either due to poor surgical repair or some unidentified internal pathology in the bowel/ bladder.

"I would say that the reasons for no improvement in my symptoms is due to bowel and nobody says anything. I believe I have got cyst in the bowel. In terms of repair, the smear people did not say anything that anything changed, or I have prolapse so I assume everything's okay." (patient 2)

"I don't know whether things have come back down again or something like that I don't know, I had a full hysterectomy but repair jobs? I don't know whether one did well." (patient 5)

"I know repair was not good, I could feel stiches turning around. (patient 1)

"I had no issues with healing, the defect is gone however, it has make vagina very tight and has been very- very uncomfortable and painful which I am not happy about." (patient 3)

"I felt my all my symptoms are due to prolapse totally." (patient 4)

4. Dissatisfaction, Frustration and Anger

Women felt that their concerns for the persistence of their symptoms after surgery had been dismissed and not properly listened and addressed. They felt frustrated and started developing disbelief in the advice offered by the medical professionals.

"They said it healed all well and held nicely up and that it's all in my head. Till now I haven't done anything about it because I thought should I be making a fuss about this?" (patient 3)

"I was actually more concerned with my haemorrhoids and bowel and no further treatment for this was offered. Very sensitive subject. I was told that there is nothing wrong. I am only constipated." (patient 2)

"I knew the repair had not worked but nobody believed me. To be honest, I just gave up and stopped going to the hospital." (patient 1).

6.5. Discussion

The outcome assessment and definition of cure is poorly defined in clinical settings (Robinson D et al., 2003; Freeman RM 2010). Objective cure has often been favoured in clinical trials whereas subjective cure is more relevant in clinical practice (Robinson

D et al., 2007). Barber et al have shown that definitions based on anatomic success have weak correlation with patient perception of outcome (Barber MD et al., 2009).

The objective data may lack the sensitivity to compare the outcomes in a meaningful way to women and so, POP outcomes are now shifting from being objective to subjective as recommended by an international collaboration (IUGA/ICS, Toozs-Hobson P et al., 2012) i.e. that the subjective outcome should be the primary one for POP surgery.

In this qualitative study we have explored women's views on prolapse surgery and the reasons for poor subjective outcome, in a cohort of women with a central sensitivity syndrome. The results suggest that most of these women presented with bowel and bladder dysfunction, back pain, dragging sensation or sexual dysfunction which are not necessarily cured by surgery. This finding is similar to previous studies (Srikrishna S et al., 2008).

Dissatisfaction is not found to be related to the type of surgical procedure but appears to relate to unrealistic expectations from surgery. For example, Finley et al in their study demonstrated that the degree of satisfaction was high if orthognathic surgery patients were well adjusted psychologically although, majority sought surgery for aesthetic reasons. Dissatisfaction was not related to sex, age or procedure. Patients who were dissatisfied tended to have higher neuroticism scores on the Eysenck Personality Inventory and had unrealistic expectations regarding post-surgical pain, numbness and swelling (Finlay PM et al.,1995).

In the current study, it would have been helpful therefore to have considered psychological factors which might be relevant for the sexual dysfunction rather than prolapse. Similarly, there may be a primary bowel problem leading to constipation/obstructed defaecation and again not due to prolapse but possibly due to rectal intussusception, which would not usually be corrected by posterior repair (as seen in 5 of 7 patients

here). If these are not identified pre-operatively and considered during selection for surgery then risk of dissatisfaction from surgery is high. Also, to note that one of the patients had recurrence of prolapse in other compartment which led to the dissatisfaction of the surgery.

Equally, there may be underlying central sensitisation responsible for a heightened perception of the dragging sensation or equally be responsible for the back pain in women with POP. Those expressing a wish for cure of these symptoms may face high level of dissatisfaction in the post-operative period if those symptoms are unaltered. This finding has been demonstrated in the study. For example: One of the patients out of 7 patients (with CSS and poor outcomes), had complaints of dragging sensation and pelvic pain along with prolapse. Her expectation from the surgery was to feel normal and have no pain. However, the pain persisted after the surgery despite of the anatomical correction of the prolapse. This results into high level of dissatisfaction and numerous clinic appointments. She was subsequently referred to pain specialist for pain management. Unfortunately, she was unavailable for the interview.

None of the women had heard about the concept of central sensitisation or the symptom severity noted in central sensitivity syndromes either at presentation or following treatment. All of them felt that poor outcome was either due to poor surgical repair (this may be correct as one of the patients presented with prolapse in different compartment but for the patient it is still a recurrence) or an internal unidentifiable pathology of bowel/ bladder.

Many felt frustrated and angry at what they described as “not been listened to” or believed regarding the persistence of their symptoms. This might be due to a lack of understanding amongst clinicians and patients of a potential underlying condition

responsible for a heightened symptom profile such as CSS (see chapter 3b, 6). Alternatively, patients might not have revealed this to the surgeons but did to the interviewer. This study is possibly the first qualitative study to explore women's views of poor surgical outcome from prolapse surgery in women with a Central Sensitivity Syndrome. The limitations are the small numbers and therefore, the data should be interpreted with caution. It is also important to consider whether all the questions (There were 5 open and 2 closed questions in the interview) were sufficient to capture adequately the views of these women. Also, there were some potential flaws in the structure of the interview-1. A semi-structured interview was used to allow the patients to elaborate and explain the issues through open ended questions but the questions were not piloted for the type of response (The questions were piloted only to check the wording of the question and not to see how much information it can extract). 2. There were 2 closed ended questions which did not help in obtaining patients opinion in depth about CS/CSS.

However, by undertaking this study, we have gained insight into women's concerns, frustration, and anger after poor outcome from surgical treatment especially when they perceive that clinicians dismiss their concerns. This same concern was raised in the Scottish Mesh enquiry (Wilkie L et al., 2017). Possibly, more emphasis needs to be placed on the pre-operative expectations and counselling of likely outcomes. Studies need to make patient reported outcomes, the primary outcome rather than the anatomical.

This appears to highlight the need for the involvement of other health professionals such as pain management specialists, psychologists, physiotherapists, bowel and continence nurses to help identify other conditions which might be responsible for the symptoms.

6.6. Conclusion

This qualitative study highlights that there is little understanding by women that central sensitisation can affect the outcome of the surgery. This might be due to a lack of awareness and understanding of this condition amongst clinicians and so inadequate counselling regarding surgical outcomes in those with a CSS. It would be interesting to assess whether women with evidence of a central sensitivity syndrome but positive outcomes post- prolapse surgery have a greater understanding of the condition (via their clinician), or whether awareness of central sensitivity syndromes might affect their decision regarding surgery or result in more realistic expectations. This is an exciting area for future research.

Summary of Findings of the thesis

Quite often patients present having had multiple re-operations for their symptoms but with little anatomical prolapse and therefore, we undertook this project to gain insight into the reasons for the poor outcomes in this group of patients. The hypothesis was that the presence of underlying CSS could be one of the factors responsible.

One of the primary findings of this project is the identification of a gap in the knowledge, understanding and awareness of central sensitivity syndrome amongst clinicians as well as patients (chapters 2 and 6). There is still disagreement amongst clinicians that patients with central sensitivity syndrome might have more bothersome symptoms compared to those without, but the study in this thesis (chapter 5) has suggested that they do. However, patients rejected the hypothesis that central sensitisation could play a role in the negative outcomes following POP surgery; they believe that a lack of improvement in their symptoms is due to poorly performed surgery or some internal pathology which has not been identified.

The second part of the study (chapter 3b) revealed that around 32% of women with pelvic organ prolapse presented to gynaecological outpatient clinics with evidence of CSS as judged by the validated CSI questionnaire and around 40% with other gynaecological problems had evidence of CSS. This suggests that CSS is common in many patients but in many is not identified.

The prospective cohort study conducted to compare the outcomes of pelvic organ prolapse surgery between two groups i.e. (those with and without CSS), found that women with CSS had less satisfaction, impression of improvement and persistence of symptoms than in those without CSS (chapter 5).

Although the predominant expectation from surgery in both groups was to become more comfortable with respect to prolapse symptoms, only 70% of women in group 1 with CSS felt their goals were met and that they were satisfied while, 95% of in group 2 without CSS felt their goals were met and were satisfied.

Only 74% of women with CSS reported the symptoms to be “very much better” or “much better” compared to 97.4% of women without. This was statistically significant. However, if we do not dichotomise the CSI data then there was no linear relationship found between CSI scores with patient satisfaction and patient global impression of improvement. This may be due to the small numbers as multiple regression works well with large number. There was positive relationship seen with pre-operative POP-SS scores and CSI scores confirming higher bother with symptoms in these group of patients.

In those with pain (not a usual symptom of prolapse), there was persistence after surgery in women with CSS with higher pain scores compared to women without CSS. These findings are likely to be of interest to clinicians as it will enable them to adequately counsel those women with CSS during consenting for the possible outcomes of the surgery while also enabling those patients to have more realistic expectations from the surgery.

Implications and conclusions

Several factors account for poor outcomes following POP surgery such as patient characteristics, co-morbidities, unrealistic expectations, high BMI, infection, smoking and poor surgical technique/surgeon factors (Vergeldt TF et al., 2015).

One of the factors identified in this study is the presence of underlying central sensitivity syndromes which might contribute to an unfavourable outcome from surgery.

There is growing evidence in orthopaedics that presence of markers of altered central pain modulation (e.g.CSS) before surgery can result in weaker outcomes and do not guarantee complete pain resolution or full functional recovery resulting in a negative emotional impact on patients (Baert I et al., 2016; Lewis GN et al., 2015).

There is nothing in the literature regarding outcomes of pelvic organ prolapse surgery in patients with CSS and as far as we know our study is the first study to demonstrate that in women with CSS, fewer have complete resolution of symptoms compared to women without CSS. This can lead to dissatisfaction and frustration.

Therefore, in those with CSS who might require surgery, pre-operative treatment of CSS could be considered to ameliorate some of the perceptual changes due to central sensitisation (Jacob NA et al., 2017). However, further research is needed to evaluate the effect of preoperative treatment of CSS on the outcomes of surgery.

Another important feature highlighted in the qualitative part of the thesis is that patients perceive that some surgeons do not listen or believe their concerns as evidenced by some women's statements. This could result in challenging consultations and disengagement by the patient with perceptions that the clinician thinks that "the symptoms were all in their head" (Sharpe M 2013) and the poor outcome has nothing to do with the surgery which in many cases might have produced a good anatomical result. However, women with CSS in the qualitative study did not feel that the poor outcome was due to altered pain modulations but due to poorly performed surgery.

There are clearly gaps in the awareness and understanding of CSS and CS by both clinicians and patients. It might, therefore, be important to screen women for CSS and educate them about the condition so that they have a better understanding of the cause of their bothersome symptoms. This might help surgeons to better counsel patients on the possible outcomes. This might also impact on the decision to proceed with surgery

or not. Further work to replicate our findings will be required before this form of screening is undertaken.

In addition, health care professionals need to be educated about this topic to empower them with the ability to manage women with these conditions.

Limitations

The current project contains a number of limitations. Firstly, the clinician survey, like many surveys had a low response rate (of 35%).

Secondly, in the prospective study, measurement of pain perception was undertaken with the help of SF-MPQ (see pg.114) and no quantitative sensory testing (e.g. pain mapping) was done to assess the severity of pain sensitisation (although POP rarely produces acute pain but rather heaviness or dragging). The numbers were small and there was a relatively short period of follow-up (chapter 5).

In chapter 5, the study was powered on the POP-SS as there is now more emphasis on capturing patient related outcomes of surgery to understand the expectations from the recipients perspective.

The CSI questionnaire used to identify women with CSS is a validated questionnaire and there were no previous studies to evaluate women with POP for underlying CSS to help with a more robust power calculation. However, our data might help power a larger study.

Another limitation was that few patients had post-operative POPQ evaluation due to either telephone follow up or refusal of patients to be examined vaginally at the time of follow up. The POPQ data was not completed by an independent researcher which might result in observer bias. Overall this would be likely to have only a minor impact on findings so far as the POPQ was a secondary outcome of the study.

In the qualitative study, the limitation was the small numbers and so the data might not generalisable and so should be interpreted with caution. It is also unknown whether the questions were sufficient to capture adequately the views of these women and as the interviews were undertaken sometime after surgery and therefore the answers might be affected by recall bias.

Recommendations

POP significantly affects a woman's quality of life and results of treatment can be unpredictable It is important to identify risk factors responsible for poor outcome after surgery and the findings of our study suggest that patients with underlying CSS can be one such group. Therefore, screening women for CSS prior to undertaking surgery for POP might be a useful way to identify and subsequently counsel patients. A broader therapeutic approach in terms of physiotherapy and cognitive treatment should be actively considered in these women especially if there are bothersome symptoms but little prolapse objectively e.g. stage 1 or 2 prolapse.

Before proceeding with surgery in such patients, a trial of vaginal pessary could be undertaken to assess the impact of prolapse reduction on their symptoms before considering surgery. If no improvement is noted then surgery might not help, whereas if the pessary helps then surgery can be offered (or alternatively to continue with the pessary).

Further studies should be designed with long-term follow up and adequate sample size (as calculated in chapter 5)- 1. To assess the impact of CSS on pelvic organ prolapse surgery and 2.To evaluate the effect of desensitisation by pre-surgical pharmacologic or non-pharmacological intervention on pop surgery in order to provide guidance on how to best manage women with the presence of POP and CSS. There is likely to be a

role for physiotherapists and psychologists in the management of these patients both before and after surgery.

Finally, both care providers and women need to be educated about CSS and clinicians need to know how to assess and manage the various manifestation of central sensitisation. In the short term, our evidence suggests that the validated questionnaire CSI could be used before a patient is considered for pelvic organ prolapse surgery but further research is required to optimise its use in this clinical arena.

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APPENDICES

Appendix 1: Central Sensitisation Inventory

Please circle the best response to the right of each statement.						
1	I feel unrefreshed when I wake up in the morning.	Never	Rarely	Sometimes	Often	Always
2	My muscles feel stiff and achy.	Never	Rarely	Sometimes	Often	Always
3	I have anxiety attacks.	Never	Rarely	Sometimes	Often	Always
4	I grind or clench my teeth.	Never	Rarely	Sometimes	Often	Always
5	I have problems with diarrhoea and/or constipation.	Never	Rarely	Sometimes	Often	Always
6	I need help in performing my daily activities.	Never	Rarely	Sometimes	Often	Always
7	I am sensitive to bright lights.	Never	Rarely	Sometimes	Often	Always
8	I get tired very easily when I am physically active.	Never	Rarely	Sometimes	Often	Always
9	I feel pain all over my body.	Never	Rarely	Sometimes	Often	Always
10	I have headaches.	Never	Rarely	Sometimes	Often	Always

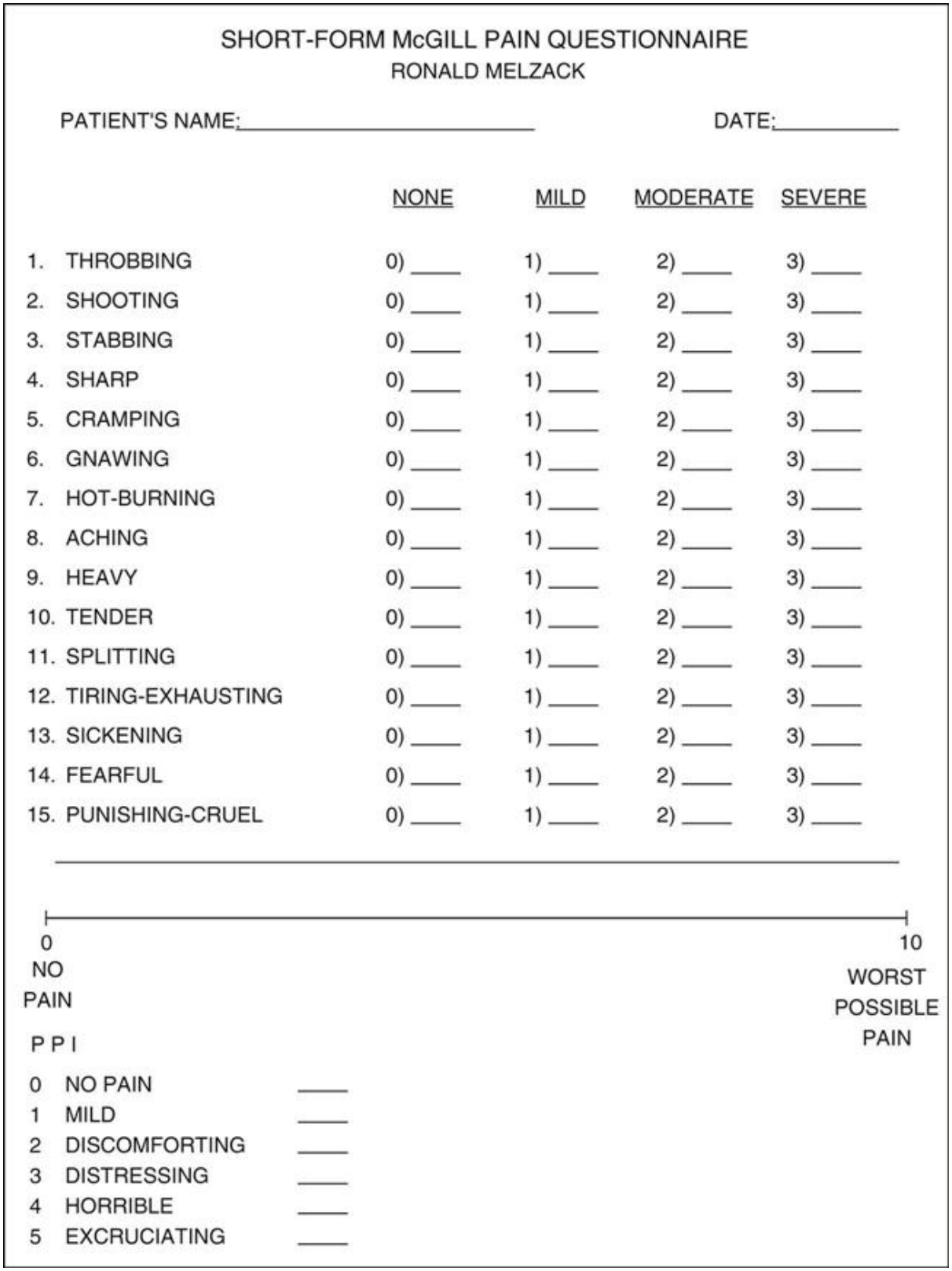
11	I feel discomfort in my bladder and/or burning when I urinate.	Never	Rarely	Some-times	Of-ten	Al-ways
12	I do not sleep well.	Never	Rarely	Some-times	Of-ten	Al-ways
13	I have difficulty concentrating.	Never	Rarely	Some-times	Of-ten	Al-ways
14	I have skin problems such as dryness, itchiness or rashes.	Never	Rarely	Some-times	Of-ten	Al-ways
15	Stress makes my physical symptoms get worse.	Never	Rarely	Some-times	Of-ten	Al-ways
16	I feel sad or depressed.	Never	Rarely	Some-times	Of-ten	Al-ways
17	I have low energy.	Never	Rarely	Some-times	Of-ten	Al-ways
18	I have muscle tension in my neck and shoulders.	Never	Rarely	Some-times	Of-ten	Al-ways
19	I have pain in my jaw.	Never	Rarely	Some-times	Of-ten	Al-ways
20	Certain smells, such as perfumes, make me feel dizzy and nauseated.	Never	Rarely	Some-times	Of-ten	Al-ways
21	I have to urinate frequently.	Never	Rarely	Some-times	Of-ten	Al-ways
22	My legs feel uncomfortable and restless when I am trying to go to sleep at night.	Never	Rarely	Some-times	Of-ten	Al-ways
23	I have difficulty remembering things.	Never	Rarely	Some-times	Of-ten	Al-ways
24	I suffered trauma as a child.	Never	Rarely	Some-times	Of-ten	Al-ways
25	I have pain in my pelvic area.	Never	Rarely	Some-times	Of-ten	Al-ways
					To-tal=	

Central Sensitization Inventory: Part B

Have you been diagnosed by a doctor with any of the following disorders? Please check the box to the right for each diagnosis and write the year of the diagnosis.				
		NO	**YES**	**Year Diagnosed**
1	Restless Leg Syndrome			
2	Chronic Fatigue Syndrome			
3	Fibromyalgia			
4	Temporomandibular Joint Disorder (TMJ)			
5	Migraine or tension headaches			
6	Irritable Bowel Syndrome			
7	Multiple Chemical Sensitivities			

8	Neck Injury (including whiplash)			
9	Anxiety or Panic Attacks			
10	Depression			

Appendix 2: McGill Pain Questionnaire



SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME:_____ DATE:_____

	NONE	MILD	MODERATE	SEVERE
1. THROBBING	0) ____	1) ____	2) ____	3) ____
2. SHOOTING	0) ____	1) ____	2) ____	3) ____
3. STABBING	0) ____	1) ____	2) ____	3) ____
4. SHARP	0) ____	1) ____	2) ____	3) ____
5. CRAMPING	0) ____	1) ____	2) ____	3) ____
6. GNAWING	0) ____	1) ____	2) ____	3) ____
7. HOT-BURNING	0) ____	1) ____	2) ____	3) ____
8. ACHING	0) ____	1) ____	2) ____	3) ____
9. HEAVY	0) ____	1) ____	2) ____	3) ____
10. TENDER	0) ____	1) ____	2) ____	3) ____
11. SPLITTING	0) ____	1) ____	2) ____	3) ____
12. TIRING-EXHAUSTING	0) ____	1) ____	2) ____	3) ____
13. SICKENING	0) ____	1) ____	2) ____	3) ____
14. FEARFUL	0) ____	1) ____	2) ____	3) ____
15. PUNISHING-CRUEL	0) ____	1) ____	2) ____	3) ____

0 NO PAIN — 10 WORST POSSIBLE PAIN

P P I

0 NO PAIN ____
1 MILD ____
2 DISCOMFORTING ____
3 DISTRESSING ____
4 HORRIBLE ____
5 EXCRUCIATING ____

Appendix 3: PGI-I

PGI-I FOR PELVIC ORGAN PROLAPSE

Study number ☐ ☐☐☐

Date ☐☐☐☐☐☐☐☐ (d d m m y y y y)

Age ☐☐

Check the number that best describes how your post-operative condition is now compared with, how it was before you had the surgery

1. Very much better ☐
2. Much better ☐
3. Little better ☐
4. No change ☐
5. A little worse ☐
6. Much worse ☐
7. Very much worse ☐

Appendix 4: POP-SS

Section A | Prolapse symptoms and their effects

Prolapse is a common condition affecting the normal support of the pelvic organs, which results in descent or 'dropping down' of the vaginal walls and/or the pelvic organs themselves. This can include the bladder, the bowel and the womb. Symptoms are usually worse on standing up and straining (e.g. lifting, coughing or exercising) and usually better when lying down and relaxing.

Prolapse may cause a variety of problems. We are trying to find out how many women experience problems from their prolapse, and how much bother it causes. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the **PAST FOUR WEEKS**. ***(Please tick one box in each row)***

How often during the last four weeks have you had the following symptoms:		Never	Occasion-ally	Some-times	Most of the time	All of the time
A1	a feeling of something coming down from or in your vagina?	☐	☐	☐	☐	☐
A2	an uncomfortable feeling or pain in your vagina which is worse when standing?	☐	☐	☐	☐	☐
A3	a heaviness or dragging feeling in your lower abdomen (tummy)?	☐	☐	☐	☐	☐
A4	a heaviness or dragging feeling in your lower back?	☐	☐	☐	☐	☐
A5	a need to strain (push) to empty your bladder?	☐	☐	☐	☐	☐
A6	a feeling that your bladder has not emptied completely?	☐	☐	☐	☐	☐
A7	a feeling that your bowel has not emptied completely?	☐	☐	☐	☐	☐
A8	which of the symptoms above (questions A1 to A7) causes you the most bother?	☐			Not applicable	☐

Please enter a number from 1 to 7 in the box, or tick 'Not applicable'

Appendix 5: Questions used for survey – chapter 2

Q1- Describe your role -

Role

Gynaecologist with special interest in urogynaecology

Subspecialist urogynaecologists

General Gynaecologists

Physiotherapist

Incontinence specialist nurse

General practitioner

Q2- How often do you see patients with pelvic organ prolapse complaining of dragging sensation rather than bulge?

Frequency

Rarely (once in 2-3 months)

Occasionally (once in a month)

Frequently (every week)

Almost always (every patient)

Q3- In your practice how often do you see patients whose symptoms of prolapse are out of proportion to/ with degree of prolapse?

Frequency

Rarely (once in 2-3 months)

Occasionally (once in a month)

Frequently (twice in a month)

Almost always (every week)

Q4- Do you believe that there is an element of central sensitisation in women where their symptoms are out of proportion to the objective prolapse?

Yes

No

Do not Know

Q5- Do you believe that women with Fibromyalgia, chronic fatigue syndrome, ME or some vaginal pain have worse symptoms than women who do not have these conditions?

Yes

No

Do not Know

Q6a- Have you heard the term Central sensitivity syndrome?

Yes

No

Q6b Please circle the following conditions that can contribute to central sensitisation syndrome.

Conditions

Fibromyalgia

Chronic fatigue syndrome

Migraine

Anxiety

Depression

Neck whiplash injury

Temporomandibular joint dysfunction

All of the above

Appendix 6: CONSENT FORM (Study 2/3)- version2, 8/11/13

TITLE: "An Investigation of the impact of Central Sensitisation in women with symptoms of pelvic floor dysfunction**."**

Name of Researchers: Prof Freeman, Dr Monika Vij, Mr Bombieri, Dr Anupreet dua, Dr Davies, Dr Madhu

Please initial the boxes

1 I confirm that I have read and understand the information sheet (Version -1) for the above study and have had the opportunity to ask questions. ☐

2 I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. ☐

3. I am willing to allow access to my medical records by authorized people but understand that strict confidentiality will be maintained. The purpose of this is to ensure that the study is being carried out correctly. ☐

All documents and forms will be kept in a locked cabinet in a secure research office at Derriford Hospital. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

4 I agree to take part in the above study. ☐

5 I agree to take part in the interview. ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature

(one copy for patient, one for researcher, one for medical notes)

Appendix 7: Questions for interview- (chapter 6)

1. What were your symptoms?
2. What were your expectations from the surgery?
3. How did you feel the surgery go?
4. Why do you think that your symptoms have not improved?
5. What do you think is the reason behind no improvement in your symptom after surgery?
6. Do you feel that persistence of your symptoms is something to do with your nerves?
7. Have you ever heard about central sensitisation or central sensitivity syndromes before?

Appendix 8: Ethics Approval letter

The letter is attached.