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# CENTRAL SENSITIZATION SYNDROME IN PATIENTS WITH PELVIC ORGAN PROLAPSE - MECHANISMS, DIAGNOSTICS, AND THERAPEUTIC APPROACHES

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## ABSTRACT

**Background:** Central Sensitization Syndrome (CSS) is increasingly recognized as a critical contributor to chronic pelvic pain in women with pelvic organ prolapse (POP). The coexistence of mechanical dysfunction and altered central pain modulation complicates diagnosis and management, requiring a multidimensional approach that integrates neurobiological, hormonal, and psychosocial perspectives.

**Objective:** To analyze the mechanisms of central sensitization in women with pelvic organ prolapse, review current diagnostic methods, and evaluate therapeutic strategies based on recent scientific evidence.

**Methods:** A narrative evidence-based review was conducted using PubMed, Scopus, and Web of Science databases for publications from 2015 to 2024. Studies addressing the mechanisms, diagnosis, and treatment of central sensitization in pelvic organ prolapse or related chronic pelvic pain syndromes were included. Data were synthesized qualitatively with critical appraisal of methodological rigor and clinical relevance.

**Results:** The literature confirms that chronic pain in women with POP often results from maladaptive neuroplasticity and central hypersensitivity rather than from anatomical defects alone. Estrogen deficiency, neuroinflammation, and prolonged nociceptive stimulation act synergistically to maintain central excitability.

Effective diagnostics require a combination of clinical evaluation, validated questionnaires, quantitative sensory testing, and neuroimaging. Treatment should follow a biopsychosocial model that integrates pharmacotherapy (gabapentinoids, SNRIs, anti-inflammatory agents), physiotherapy, and psychological interventions such as cognitive-behavioral therapy. Noninvasive neuromodulation and molecular therapies targeting NMDA and TRPV1 receptors show emerging promise.

**Conclusions:** Central sensitization represents a pivotal but underdiagnosed mechanism in the pathophysiology of pelvic organ prolapse–related pain. Early identification of CSS features and implementation of individualized multimodal therapy improve pain control, functional outcomes, and quality of life. Multidisciplinary collaboration remains essential for optimizing diagnosis and treatment in this complex patient population.

**Keywords:** central sensitization syndrome, pelvic organ prolapse, chronic pelvic pain, diagnostics, physiotherapy, cognitive-behavioral therapy, multimodal treatment.

# INTRODUCTION

Pelvic organ prolapse (POP) is one of the most common forms of pelvic floor dysfunction in women, particularly in the postmenopausal period, and is associated with a marked decline in quality of life due to pain, discomfort, and functional impairment. Epidemiological data indicate that the prevalence of symptomatic POP reaches 30–50% among women over 70 years of age [1, 2]. Recent findings suggest that, in a subset of patients, pain symptoms cannot be explained solely by mechanical factors but are linked to impaired central pain modulation and the development of central sensitization[3, 4].

Central Sensitization Syndrome (CSS) is a pathological condition characterized by increased excitability of central nociceptive pathways, leading to chronic pain perception even in the absence of peripheral tissue injury [4, 5]. This mechanism plays a crucial role in the formation of chronic pelvic pain, including that associated with POP. Studies have shown that women with POP more frequently exhibit hyperalgesia, allodynia, and generalized sensory hypersensitivity, indicating the involvement of central neuronal processes [6-8].

Understanding the role of CSS in the pathogenesis of POP has significant clinical importance, as central sensitization modifies the therapeutic response and influences the effectiveness of both surgical and conservative interventions. The integration of neurobiological, hormonal, and psychosocial factors into diagnostic and therapeutic strategies brings clinical practice closer to a personalized approach for this patient group [9-11].

Despite the growing body of research on chronic pelvic pain, the influence of central sensitization in pelvic organ prolapse remains insufficiently studied. The present review aims to systematize the current knowledge and identify future research directions.

The objective of this study is to analyze current evidence on the mechanisms, diagnostic methods, and therapeutic possibilities of Central Sensitization Syndrome in women with Pelvic Organ Prolapse.

The following research questions are addressed:

1. What neurobiological and hormonal mechanisms underlie the development of central sensitization in women with pelvic organ prolapse?
2. Which diagnostic methods most accurately identify signs of CSS in this patient group?
3. Which therapeutic approaches, including physiotherapy, pharmacological, and psychosocial interventions, demonstrate proven effectiveness in managing POP associated with CSS?
4. What research directions appear most promising for further exploration of the role of central sensitization in the pathogenesis of pelvic organ prolapse?

Thus, this review seeks to elucidate the clinical and pathophysiological relationship between POP and CSS, assess the current state of evidence, and formulate recommendations for optimizing diagnostic and management strategies based on up-to-date scientific data [1-11].

# METHODS

## DESIGN AND AIM

This work was conducted as a narrative evidence-based review. Its objective was to synthesize current data on the mechanisms of central sensitization in women with pelvic organ prolapse, to analyze diagnostic approaches, and to summarize existing therapeutic strategies. No meta-analysis was performed, and the structure follows the standards for narrative biomedical reviews.

### Sources and Search Strategy

The literature search was performed in PubMed, Scopus, and Web of Science databases for the period from 2015 to 2024. The following keywords and their combinations were used: central sensitization, pelvic organ prolapse, chronic pelvic pain, diagnostics, treatment, physiotherapy. Boolean operators AND and OR were applied. Only peer-reviewed articles in English were included.

### Inclusion Criteria

Studies addressing the mechanisms, diagnosis, or treatment of central sensitization in pelvic organ prolapse or other chronic pelvic pain syndromes were included. Narrative and systematic reviews, randomized controlled trials, observational, and prospective studies with clearly described design and inclusion criteria were considered eligible.

### Exclusion Criteria

Experimental animal studies, non-peer-reviewed materials, publications prior to 2015, short communications, and conference abstracts were excluded.

### Selection and Data Extraction

All records were screened manually. Titles and abstracts were first reviewed for relevance, followed by full-text evaluation. The extracted information included study design, sample size and characteristics, diagnostic criteria, investigated mechanisms of central sensitization, main results, and clinical conclusions. Data synthesis was qualitative rather than quantitative.

### Synthesis and Quality Assessment

The findings were integrated with a critical appraisal of the reliability and applicability of evidence. Formal risk-of-bias assessment was not conducted due to the heterogeneity of available data. The level of evidence was evaluated experientially, considering clinical relevance and methodological transparency.

### Selected Literature

A total of 41 publications met the inclusion criteria. The final selection comprised recent clinical guidelines, systematic and critical reviews, randomized controlled trials, and observational studies. Most sources were published between 2015 and 2024, with a few earlier works included because of their high scientific value. Several incomplete bibliographic entries were identified and require clarification.

### General Limitations

The main limitation of the review is the heterogeneity of methods used to assess pain and central sensitization, as well as differences in study populations. Despite this, the analyzed material reflects the current state of knowledge on central sensitization in pelvic organ prolapse and provides a comprehensive understanding of this clinical phenomenon.

# RESULTS

## MECHANISMS OF CENTRAL SENSITIZATION IN PELVIC ORGAN PROLAPSE

Pelvic organ prolapse (POP) is a common condition, particularly among women who have undergone vaginal deliveries, those with obesity, and postmenopausal women. It is characterized by the descent or prolapse of pelvic organs, leading to mechanical, urological, gastrointestinal, and sexual symptoms. Increasing evidence suggests that, in a subset of patients with POP, pain symptoms may originate not only from peripheral mechanisms but also from central processes associated with central sensitization [12-14].

Studies have demonstrated that women with POP more frequently exhibit symptoms characteristic of central sensitization, such as tactile hypersensitivity, chronic muscular tension, and sexual dysfunction. This phenomenon may be exacerbated by chronic mechanical strain, as well as by hormonal disturbances that impair the function of pelvic muscles and connective tissue [3, 11].

Based on a meta-analysis in Chinese women, the estimated prevalence of symptomatic POP increased from ≈ 4.8% in women aged 20-29 to ≈ 28.2% in women aged ≥ 70 [1]. An Italian cross-sectional study reported 9.7% prevalence in women aged 20-39 and 49.7% in women over 80 [2]. Based on these representative data, the values used in Tables 1. These estimates reflect observed trends demonstrating an approximate sixfold increase in prevalence from early adulthood to late postmenopausal age.

These disorders are classified according to the anatomical compartment involved in the prolapse. The following types are distinguished: (1) cystocele - descent of the anterior vaginal wall and urinary bladder; (2) rectocele - descent of the posterior vaginal wall and rectum; (3) enterocele - herniation involving the small intestine; and (4) uterine or cervical prolapse, or, in women after hysterectomy, vaginal vault prolaps [15, 16].

The severity of prolapse is assessed using the Pelvic Organ Prolapse Quantification (POP-Q) system, which evaluates the extent of organ descent relative to the hymenal ring [3].

## TREATMENT OF POP

The therapeutic approach to pelvic organ prolapse depends on the stage of prolapse and the severity of symptoms. In stages I-II according to the POP-Q scale, for patients with mild symptoms or for the prevention of progression, conservative management is recommended. This includes pelvic floor muscle rehabilitation (Kegel exercises, biofeedback), the use of pessaries, and lifestyle modifications such as weight reduction and avoidance of heavy lifting [3].

In stages III-IV, when symptoms are severe and conservative treatment proves ineffective, surgical intervention is indicated. Surgical options include anterior and posterior colporrhaphy, sacrocolpopexy, and uterine or vaginal vault suspension using synthetic or autologous mesh materials [17]. The choice of surgical technique depends on the patient’s age, sexual activity, comorbidities, and individual preferences.

## PREVENTION OF POP

Prevention of pelvic organ prolapse is based on the modification of risk factors and the strengthening of pelvic floor support structures. Patient education regarding pelvic floor muscle exercises (Kegel training) is of fundamental importance and should begin during pregnancy and the postpartum period. Weight reduction, prevention of chronic constipation, proper lifting techniques, and treatment of chronic cough also play a significant role in reducing the risk of POP[18].

In women with identified risk factors, early use of pessaries may be considered to reduce the mechanical load on pelvic floor structures [17]. As in treatment, the choice of preventive strategy should take into account the patient's age, sexual activity, comorbidities, and individual preferences.

Pelvic organ prolapse (POP) is frequently associated with symptoms of central sensitization syndrome (CSS), contributing to chronic pain complaints. Central sensitization syndrome is defined as a pathological hypersensitivity of the central nervous system, resulting from persistent alterations in its ability to modulate sensory input, which leads to an exaggerated perception of pain, even in response to physiologically non-noxious stimuli [2, 4]. This phenomenon manifests as hyperalgesia, allodynia, and generalized somatic hypersensitivity [6].

These symptoms are often widespread and may significantly impair quality of life. Affected patients report pain in multiple body regions, disproportionate to any localized anatomical abnormalities, indicating the involvement of central mechanisms. A hallmark feature is the temporal variability in symptom intensity, along with hypersensitivity to emotional stimuli, fatigue, and the co-occurrence of other central sensitivity syndromes such as irritable bowel syndrome and fibromyalgia [4, 6, 8]. These manifestations are characteristic of disorders with a central component and point to neuronal reorganization within the central nervous system [2, 7].

## MUSCLE DYSFUNCTION AND PELVIC FLOOR WEAKNESS

Chronic overload and sustained tension of the pelvic floor muscles, which are characteristic of pelvic organ prolapse, result in persistent activation of nociceptors. This condition can lead to prolonged stimulation of pain pathways and progression toward central sensitization. Moreover, chronic muscular tension and compensatory movement patterns may contribute to alterations in muscle coordination, reduced pelvic mobility, and pain arising from soft tissue overload [19].

Studies indicate that imbalance between the activity of superficial and deep pelvic floor muscles results in impaired stabilization, which exacerbates pain symptoms and reinforces central sensitization mechanisms [1].

## CENTRAL NERVOUS SYSTEM PLASTICITY

Plastic changes within central nervous system synapses, including enhanced activation of NMDA receptors and long-term potentiation (LTP), result in increased nociceptive transmission and a lowered pain threshold. Reorganization of neuronal connections may lead to the persistence of maladaptive pain patterns and difficulty in their modulation [20].

Neuroimaging studies have demonstrated heightened activation of brain regions involved in pain processing,

including the thalamus, insular cortex, and anterior cingulate gyrus, confirming the presence of neuroplastic alterations in the course of CSS[2]. These changes contribute to the intensification of symptoms such as hyperalgesia and allodynia.

## INFLUENCE OF SEX HORMONES

In postmenopausal women, the decline in estrogen levels may reduce the efficacy of endogenous pain inhibitory mechanisms. Estrogens play a crucial role in modulating nervous system function by influencing the activity of GABAergic, NMDA, and serotonergic receptors. Their deficiency can lead to diminished pain inhibition and heightened nociceptive sensitivity [21].

Furthermore, hormonal fluctuations affect the hypothalamic-pituitary-adrenal axis and lower the pain tolerance threshold, rendering perimenopausal women more susceptible to the development of CSS symptoms [3]. Hormonal imbalances enhance vulnerability to CSS through their impact on neurotransmitter systems and central antinociceptive pathways.

## MECHANISMS OF CENTRAL SENSITIZATION

Central sensitization syndrome (CSS) denotes a persistent increase in the excitability of central nociceptive pathways. In chronic pain states, maladaptive synaptic plasticity and neuroinflammation lead to sustained neuronal hyper responsiveness and exaggerated pain perception. Activated microglia and astrocytes release pro inflammatory cytokines and chemokines, acting as potent neuromodulators that drive hyperalgesia and allodynia. The interplay of neurotrophic factors, purinergic receptors, persistent glutamatergic transmission and long term potentiation underpins the resilience of the pain network and highlights the need for therapies that target both neuronal and glial mechanisms [22].

## DIAGNOSTICS

The diagnosis of central sensitization syndrome (CSS) in patients with pelvic organ prolapse (POP) requires a multidisciplinary approach encompassing clinical assessment, screening questionnaires, sensory testing, and neuroimaging techniques [6, 9, 10, 23]. In clinical practice, the most widely used tools include the Central Sensitization Inventory (CSI), which allows preliminary evaluation of CSS-related symptoms; quantitative sensory testing (QST), which measures pain thresholds in response to various stimuli (mechanical, thermal); and functional brain imaging modalities such as functional magnetic resonance imaging (fMRI) and somatosensory evoked potentials (SEPs), both of which provide insights into altered pain processing within the central nervous system [24].

SEPs are an electrodiagnostic method that records electrical responses in the brain following peripheral nerve stimulation. In patients with suspected CSS, SEP testing often reveals altered somatosensory cortical activation patterns, delayed latencies, and reduced signal amplitudes, indicating central abnormalities in sensory processing. This method may be particularly valuable for differentiating central versus peripheral pain mechanisms and for evaluating the effectiveness of neuromodulatory therapies [9].

fMRI enables visualization of brain activity changes by detecting alterations in cerebral blood flow in response to nociceptive stimuli, thereby identifying and analyzing structures involved in pain processing. In patients with CSS, increased activation of the thalamus, insular cortex, and anterior cingulate gyrus has been observed, confirming the presence of neuroplastic changes within the nervous system and serving as a useful adjunct in distinguishing CSS from other forms of chronic pain [9].

Additionally, psychosocial assessment tools—such as the Pain Catastrophizing Scale (PCS), the Hospital Anxiety and Depression Scale (HADS), and other validated questionnaires—play a crucial role in identifying central components of chronic pain. Stress, anxiety, and maladaptive pain beliefs can amplify central sensitization processes. Incorporating psychosocial evaluation with clinical and neurophysiological assessments enhances diagnostic accuracy and facilitates a more individualized therapeutic approach [10, 11, 25].

Quantitative Sensory Testing (QST) involves the controlled application of mechanical, thermal, or chemical stimuli to determine sensory and pain thresholds. Patient responses are analyzed and compared to population norms [6]. To assess hyperalgesia, methods such as the Pressure Pain Threshold (PPT) and Thermal Pain Threshold (TPT) tests are commonly used.

The PPT test entails gradually increasing pressure with an algometer until the participant reports the first sensation of pain; lower threshold values indicate pain hypersensitivity. The TPT test measures the pain threshold triggered by controlled thermal stimuli (cold or heat) applied via specialized probes. Reduced thresholds in these tests suggest the presence of hyperalgesia and support the identification of a central component in the pain mechanism [6, 7, 9].

Allodynia assessment is performed using light brushing of the skin (brush allodynia) or calibrated monofilament testing (von Frey filaments). Brush allodynia involves gently stroking the skin with a soft brush or gauze and assessing the pain response to this normally non-noxious tactile stimulus. In von Frey testing, calibrated filaments of varying diameters and force are applied to identify abnormal pain responses to light pressure. In patients with CSS, even minimal stimuli may elicit discomfort or pain, indicative of central sensory hypersensitivity. These tests are particularly valuable for differentiating mechanical allodynia and monitoring therapeutic progress [7, 9].

In patients with POP and concomitant chronic pain, quantitative sensory testing (QST) facilitates the differentiation between peripheral and central pain components, identification of pain hypersensitivity mechanisms (e.g., generalized hyperalgesia), and monitoring of the effectiveness of non-pharmacological interventions such as physiotherapy [9, 10].

Additionally, during transvaginal examinations, women with POP and CSS may report increased pain or discomfort, even in the absence of significant structural abnormalities. These symptoms are often nonspecific and may include burning sensations, pelvic pressure, pain radiating to the lumbosacral region, or dyspareunia. Studies have shown that palpatory sensitivity of the pelvic floor muscles (e.g., *levator ani*) is significantly higher in patients with a central pain component, and that the examination itself may exacerbate pain symptoms by activating sensitized nociceptive pathways [26].

Consequently, the interpretation of examination findings must consider the patient's neurophysiological and psychological context. Communication during the examination should be empathetic and mindful of the potential impact of prior trauma or painful experiences [12, 27]. Such responses are consistent with the mechanism of central sensitization, wherein normally non-noxious stimuli are perceived as painful due to heightened excitability of the central nervous system [3, 27]. Psychological factors, such as anxiety and pain anticipation, may further amplify discomfort during the examination, complicating clinical assessment and underscoring the necessity of integrating a biopsychosocial approach (Table 2) [28, 29].

## THERAPEUTIC STRATEGIES

The treatment of central sensitization requires a multimodal approach targeting both the underlying mechanisms and the associated symptoms. Current therapeutic strategies encompass pharmacological, non-pharmacological, and emerging interventions.

Pharmacological Therapies Centrally Acting Agents

Drugs such as gabapentin, pregabalin, and serotonin-norepinephrine reuptake inhibitors (SNRIs) — including duloxetine and venlafaxine — are commonly employed to mitigate central sensitization by modulating neurotransmitter release, reducing neuronal hyperexcitability, and enhancing endogenous pain-inhibitory mechanisms. Their efficacy has been confirmed in studies involving patients with chronic pelvic pain and fibromyalgia, particularly in cases presenting with hyperalgesia and allodynia [4, 11, 30, 31].

Anticonvulsants: Agents such as carbamazepine and lamotrigine, although less frequently used in the management of CSS, possess the ability to suppress excessive neuronal activity and may be considered in refractory cases [32, 33].

Corticosteroids and Anti-Inflammatory Agents: These are primarily utilized in scenarios where concomitant inflammatory processes are suspected. Such agents exert their effects by attenuating glial cell activation and inhibiting the release of pro-inflammatory cytokines, which may exacerbate central sensitization [5, 34].

## NON-PHARMACOLOGICAL THERAPIES

### Cognitive-Behavioral Therapy (CBT)

CBT is a structured form of psychological therapy focused on identifying and modifying maladaptive thoughts and behaviors related to pain. It enhances patients' coping abilities with chronic pain by reshaping pain-related beliefs, reducing catastrophizing, and fostering adaptive strategies such as relaxation techniques and gradual physical activity pacing.

A standard CBT program typically consists of 8 to 16 weekly sessions delivered over approximately 10-12 weeks. Depending on symptom severity and the presence of comorbid psychological disorders, therapy may be extended or supplemented with booster sessions. CBT also facilitates the recognition and modification of maladaptive cognitive patterns, supporting adaptation to chronic pain [11, 35, 36]. Clinical studies demonstrate that CBT effectively reduces pain intensity, improves quality of life, and enhances psychological functioning in patients with CSS [11, 35].

### Neurostymulation Techniques

Techniques such as transcranial magnetic stimulation (TMS), spinal cord stimulation (SCS), transcranial direct current stimulation (tDCS), and transcutaneous electrical nerve stimulation (TENS) have demonstrated promising effects in managing chronic pain of central origin. TMS modulates cortical excitability and pain network activity, particularly in the prefrontal cortex and cingulate gyrus. SCS acts at the spinal level by inhibiting nociceptive transmission and engaging segmental pain-inhibitory mechanisms. tDCS modulates cortical activity, influencing nociceptive processing and enhancing outcomes when combined with CBT or rehabilitation. TENS is a readily applicable ambulatory technique that exerts analgesic effects through Aβ fiber activation and increased endorphin release. These therapies are considered safe, and their effectiveness is enhanced with appropriate parameter selection and individualized treatment planning [27, 35-37].

## EXERCISE AND REHABILITATION

Rehabilitation plays a pivotal role in managing patients with CSS, particularly in the context of coexisting pelvic organ prolapse. Therapeutic programs incorporate pelvic floor muscle training (PFMT), mindful movement practices, manual therapy (soft tissue mobilization, trigger point therapy), breathing techniques (diaphragmatic training, breathing biofeedback), and functional exercise integration [38].

Pelvic floor exercises improve muscle strength, endurance, and coordination while supporting neuromodulatory processes within the central nervous system. They also significantly reduce symptoms of POP, especially in early stages. Regular activation and strengthening of the pelvic floor muscles can prevent further organ descent, enhance pelvic stability, and improve quality of life by alleviating sensations of pelvic pressure, vaginal fullness, or urinary incontinence. Supervised training facilitates functional adaptation and optimizes lower trunk biomechanics [5, 23, 39].

Consistent PFMT activates type I and type II muscle fibers responsible for pelvic support and continence control. Additionally, it improves proprioception, thereby enhancing functional control and reducing pain episodes. Both isometric and dynamic exercises are recommended, often supplemented with biofeedback or electrical stimulation to optimize muscle recruitment and improve patient adherence [39].

Mindful movement practices aid relaxation and reduce neuromuscular tension, while manual therapy alleviates palpation-related pain and improves range of motion. Breathing techniques reduce autonomic arousal, mitigating anxiety and stress levels [23, 39]. Regular exercise enhances proprioceptive feedback, improves muscle control, and reduces excessive tension, contributing to chronic pain reduction. Optimal outcomes are achieved with programs supervised by physiotherapists trained in chronic pain and pelvic floor dysfunction management. Programs should last at least 8-12 weeks, with individually tailored techniques. Gradual exercise progression combined with adjunctive physiotherapeutic modalities improves functional outcomes and reduces pain severity in patients with central sensitization [11, 23].

## INNOVATIVE THERAPEUTIC STRATEGIES

### Targeted Molecular Therapies

Contemporary pharmacological approaches focus on selectively modulating molecular mediators responsible for the development and maintenance of central sensitization. These include inhibitors of the system xc−, NMDA receptor antagonists, TRPV1 and P2X3 receptor blockers, as well as Nav1.7 sodium channel inhibitors. Additionally, research on neurokinin-1 receptor antagonists, IL-1β and TNF-α cytokine inhibitors, monoclonal antibodies, and nanotechnology-based drug delivery systems targeting central nervous system structures aims to enhance therapeutic selectivity and minimize adverse effects [5, 9, 37].

### Non-Invasive Modulation of Brain Plasticity

Techniques such as virtual reality (VR) and cognitive training show potential in reducing pain hypersensitivity by influencing neuroplasticity and pain-processing networks. VR enables multisensory patient engagement and distraction from pain, whereas cognitive training strengthens cognitive control over pain responses and supports executive and emotional functioning. Both methods can serve as adjuncts to conventional therapies, particularly in patients with a pronounced central component and coexisting affective disorders (Table 3-4) [27, 37].

### Clinical Implications and Future Directions

Central sensitization is a common mechanism underlying various chronic pain conditions, including fibromyalgia, chronic low back pain, and neuropathic pain. Despite significant advances in understanding its pathophysiology, the development of targeted therapies remains challenging. Future research should focus on

elucidating the molecular and functional mechanisms of central sensitization and exploring novel therapeutic strategies aimed at improving patient outcomes [2, 4, 5].

## DISCUSSION

Central sensitization represents a key mechanism explaining persistent pain in women with pelvic organ prolapse. Current evidence confirms that, in some patients, the severity of symptoms does not correlate with the degree of anatomical impairment, indicating the involvement of central neuronal processes in the development of chronic pain [2, 4, 6].

Several studies have demonstrated that POP is associated with neuroplastic changes, including increased excitability of spinal and supraspinal structures, NMDA receptor hyperactivation, and microglial involvement, all of which maintain nociceptive transmission and result in sustained hyperalgesia [4, 5, 34]. Neuroimaging findings show enhanced activation of the thalamus, insula, and cingulate cortex, confirming the reorganization of brain networks responsible for pain perception [2, 9].

The mechanisms underlying central sensitization in women with pelvic organ prolapse are complex and multifactorial. Table 1 summarizes the principal neurobiological, hormonal, inflammatory, and psychosocial factors contributing to the development and maintenance of chronic pain in this population.

*Table 1. Main mechanisms of central sensitization in pelvic organ prolapse (POP)*

| Mechanism | Key mediators and structures | Clinical manifestations | Key references |
|---|---|---|---|
| **Neuronal** | NMDA receptors, AMPA receptors, microglia, astrocytes, thalamus, insular cortex, cingulate gyrus | Hyperalgesia, allodynia, generalized sensory hypersensitivity, variability of pain intensity | [2, 4-7, 9, 34] |
| **Hormonal** | Estrogens, GABAergic, serotonergic, and glutamatergic systems, hypothalamic–pituitary–adrenal axis | Increased pain perception in postmenopausal women, decreased pain threshold, impaired endogenous pain control | [3, 11] |
| **Inflammatory** | IL-1β, TNF-α, IL-6, chemokines, xc– system, activation of glia and microglia | Chronic pain, maintenance of neuronal hyperexcitability, enhanced neuroinflammation, persistent nociceptive transmission | [5, 9, 34, 37] |
| **Psychosocial** | Stress-response axis dysfunction, pain catastrophizing, anxiety, depression, sleep disturbance | Increased subjective pain intensity, fatigue, hyperreactivity to stress stimuli, amplification of central sensitization | [10, 11, 35] |

Hormonal alterations in postmenopausal women further aggravate this process. Estrogen deficiency reduces the efficiency of endogenous antinociceptive systems and increases pain sensitivity by disrupting GABAergic, serotonergic, and NMDA receptor regulation. This mechanism explains the higher prevalence of CSS symptoms among older women with POP [40].

Peripheral factors also play a significant role. Chronic overload and functional weakness of the pelvic floor muscles lead to continuous afferent stimulation and create a feedback loop between peripheral and central pain mechanisms [1, 11]. Loss of coordination between deep and superficial muscle layers results in pelvic instability and activation of sensitized nociceptors.

Accurate diagnosis of central sensitization in patients with pelvic organ prolapse requires combining subjective and objective tools that assess both physiological and psychological dimensions of pain processing. Table 2

summarizes the most commonly used diagnostic methods and their clinical applicability.

*Table 2. Diagnostic methods for identifying central sensitization in patients with pelvic organ prolapse (POP)*

| Diagnostic method / tool | Purpose of application | Main parameters / interpretation criteria | Advantages and limitations | Key references |
|---|---|---|---|---|
| **Central Sensitization Inventory (CSI)** | Screening and quantification of central sensitization symptoms | Total score ≥ 40 suggests clinically relevant central sensitization | Easy to use; reflects subjective symptom severity; does not differentiate between central and peripheral mechanisms | [6-8, 23] |
| **Quantitative Sensory Testing (QST)** | Objective assessment of pain thresholds and sensory hypersensitivity | Measures pressure, thermal, and vibration thresholds; detects allodynia and hyperalgesia | Provides physiological data; sensitive to central changes; requires specialized equipment and trained personnel | [6, 9, 23] |
| **Functional Magnetic Resonance Imaging (fMRI)** | Visualization of brain activity and pain-related cortical reorganization | Increased activation of thalamus, insula, anterior cingulate cortex | Demonstrates neural correlates of central sensitization; limited availability, high cost | [2, 9, 34, 37] |
| **Somatosensory Evoked Potentials (SEP)** | Assessment of central conduction and cortical response to nociceptive input | Prolonged latency or increased amplitude of cortical potentials | Objective electrophysiological marker of central hyperexcitability; interpretation requires expertise | [5, 7, 30] |
| **Pain Catastrophizing Scale (PCS)** | Evaluation of cognitive–emotional pain modulation and maladaptive beliefs | High scores reflect catastrophization and enhanced pain perception | Quick to administer; correlates with pain intensity and psychological distress; subjective | [10, 11] |
| **Hospital Anxiety and Depression Scale (HADS)** | Screening for comorbid anxiety and depression influencing pain perception | Scores ≥ 8 in either subscale indicate emotional comorbidity | Identifies psychosocial amplifiers of central sensitization; limited to self-report | [10, 35] |

From a diagnostic perspective, the combination of clinical assessment, validated questionnaires (Central Sensitization Inventory, Pain Catastrophizing Scale), quantitative sensory testing, and neurophysiological methods such as SEP and fMRI is of primary importance [6-9, 23]. These approaches help differentiate central from peripheral pain mechanisms and quantify the degree of sensitization. Psychological screening using HADS and PCS further refines diagnosis by identifying catastrophizing, anxiety, and depression, which amplify pain perception [10, 11].

Effective management of women with pelvic organ prolapse and central sensitization requires an integrative, multimodal strategy. Table 3 presents the main therapeutic approaches, mechanisms of action, and current levels of evidence supporting their clinical use.

*Table 3. Therapeutic approaches for pelvic organ prolapse (POP) associated with central sensitization syndrome (CSS)*

| Therapeutic approach | Example of intervention / agent | Mechanism of action | Effectiveness and level of evidence | Main limitations | Key references |
|---|---|---|---|---|---|
| **Pharmacological therapy – neuromodulators** | Gabapentin, Pregabalin, Duloxetine | Reduction of neuronal hyperexcitability, modulation of serotonin–norepinephrine pathways | Moderate-to-high evidence for pain reduction and improved function | Sedation, dizziness, limited long-term data | [4, 11, 30, 31] |
| **Anti-inflammatory and glial modulators** | Nonsteroidal anti-inflammatory drugs (NSAIDs), minocycline | Decrease of microglial activation and cytokine-mediated neuroinflammation | Moderate evidence; beneficial in cases with inflammatory component | Gastrointestinal side effects, incomplete pain control | [5, 9, 34, 41] |
| **Physiotherapy and pelvic floor rehabilitation** | Pelvic floor muscle training, manual therapy, breathing exercises | Restoration of pelvic stability, reduction of afferent nociceptive input, modulation of central pain processing | High evidence for improved muscle function and pain relief | Requires patient adherence, variable standardization | [11, 23, 35, 39] |
| **Cognitive-behavioral therapy (CBT)** | Individual or group sessions targeting maladaptive beliefs and catastrophizing | Modification of pain perception and coping mechanisms via cognitive restructuring | High evidence for reduced catastrophizing and improved quality of life | Requires psychological support availability, subjective engagement | [11, 35, 36] |
| **Neuromodulation techniques** | Transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcutaneous electrical nerve stimulation (TENS) | Noninvasive modulation of cortical excitability and pain networks | Growing evidence; promising results in chronic pain syndromes | Limited accessibility, need for specialized equipment | [27, 35, 37] |

The management of patients with POP and CSS must be multidisciplinary. Pharmacotherapy with central neuromodulators such as gabapentin, pregabalin, and duloxetine has shown efficacy in reducing hyperalgesia and allodynia [4, 30, 31]. In refractory cases, anticonvulsants and anti-inflammatory drugs targeting glial activation may be beneficial [5, 34, 41].

Nonpharmacological interventions, particularly cognitive-behavioral therapy (CBT) and specialized physiotherapy, remain the cornerstone of long-term pain control. CBT reduces catastrophizing, improves quality of life, and restores adaptive coping strategies [11, 35, 36]. Physiotherapy programs that include pelvic floor muscle training, manual therapy, and breathing exercises not only strengthen pelvic support but also modulate

central pain processing [23, 39].

Promising therapeutic directions include noninvasive neuromodulation techniques such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcutaneous electrical nerve stimulation (TENS), which influence pain-related neuronal networks and enhance behavioral treatment outcomes [27, 35, 37]. Molecular strategies targeting NMDA, TRPV1, and P2X3 receptors, as well as monoclonal antibodies against IL-1β and TNF-α, are under investigation [5, 9, 37]. These developments open perspectives for pathogenetically oriented treatment.

Overall, the available evidence supports that successful management of women with POP and central sensitization requires the integration of biological, psychological, and social components. Early identification of CSS features and individualized therapy reduce pain severity, improve functional outcomes, and enhance quality of life [2, 3, 6, 8, 10, 11, 23, 39].

# CONCLUSIONS

Central Sensitization Syndrome is an important yet frequently underrecognized factor contributing to chronic pelvic pain in women with pelvic organ prolapse. The analysis of available literature demonstrates that pain in these patients often results not only from mechanical dysfunction and structural displacement but also from altered central pain modulation and maladaptive neuroplasticity.

The review confirms that hormonal changes, neuroinflammatory processes, and prolonged peripheral stimulation act synergistically to sustain nociceptive hypersensitivity and reinforce central sensitization mechanisms. Functional reorganization of pain-processing brain regions, including the thalamus, insula, and anterior cingulate cortex, underlies persistent hyperalgesia and allodynia, which remain disproportionate to the degree of anatomical changes.

Accurate diagnosis requires a multidisciplinary assessment combining clinical evaluation, validated questionnaires, quantitative sensory testing, and neuroimaging techniques. Psychological assessment is essential to identify catastrophizing, anxiety, and depressive symptoms that amplify central pain processing.

Therapeutic management should follow a biopsychosocial model. Pharmacological interventions such as gabapentinoids, serotonin–norepinephrine reuptake inhibitors, and anti-inflammatory agents provide symptom relief but are most effective when combined with physiotherapy and psychological therapy. Cognitive-behavioral therapy reduces maladaptive cognitive patterns and improves coping strategies, while specialized pelvic floor rehabilitation enhances neuromuscular control and modulates central pain pathways.

Emerging modalities such as noninvasive brain stimulation and molecular therapies targeting NMDA, TRPV1, and cytokine-mediated mechanisms represent promising adjuncts for the future.

Early identification of central sensitization features in women with pelvic organ prolapse and the implementation of individualized multimodal treatment substantially improve pain control, functional outcomes, and overall quality of life. The integration of biological, psychological, and rehabilitative interventions remains the cornerstone of effective and sustainable management in this patient population.

# DISCLOSURE

## AUTHORS' CONTRIBUTIONS

Conceptualization: Magdalena Barbara Kukulska, Piotr Kukulski

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## USE OF AI

Artificial intelligence (AI) tools were used to assist in literature searches and identification of peer-reviewed

scientific articles relevant to this work.

## CONFLICT OF INTEREST

The authors declare no potential conflicts of interest regarding the publication of this paper.

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# REFERENCES

1. Zielinska Z, et al.,. Chronic Pelvic Pain Syndrome among women - challenge in diagnostics and management. Current literature review. Journal of Education, Health and Sport. 2024;55:170-84.https://doi.org/10.12775/JEHS.2024.55.011
2. Eller-Smith OC, Nicol AL, Christianson JA. Potential Mechanisms Underlying Centralized Pain and Emerging Therapeutic Interventions. Front Cell Neurosci. 2018;12:35.https://doi.org/10.3389/fncel.2018.00035
3. Allaire C, Yong PJ, Bajzak K, Jarrell J, Lemos N, Miller C, et al. Guideline No. 445: Management of Chronic Pelvic Pain. J Obstet Gynaecol Can. 2024;46(1):102283.https://doi.org/10.1016/j.jogc.2023.102283
4. Ma YC, Kang ZB, Shi YQ, Ji WY, Zhou WM, Nan W. The Complexity of Neuropathic Pain and Central Sensitization: Exploring Mechanisms and Therapeutic Prospects. J Integr Neurosci. 2024;23(5):89.https://doi.org/10.31083/j.jin2305089
5. Beckers P, Belo Do Nascimento I, Charlier M, Desmet N, Massie A, Hermans E. Implication of system x(c) (-) in neuroinflammation during the onset and maintenance of neuropathic pain. J Neuroinflammation. 2024;21(1):117.https://doi.org/10.1186/s12974-024-03112-9
6. Curatolo M. Central Sensitization and Pain: Pathophysiologic and Clinical Insights. Curr Neuropharmacol. 2024;22(1):15-22.https://doi.org/10.2174/1570159x20666221012112725
7. Zheng P, Zhang W, Leng J, Lang J. Research on central sensitization of endometriosis-associated pain: a systematic review of the literature. J Pain Res. 2019;12:1447-56.https://doi.org/10.2147/jpr.S197667
8. Dahmani D, Taik FZ, Berrichi I, Fourtassi M, Abourazzak FE. Impact of central sensitization on pain, disability and psychological distress in patients with knee osteoarthritis and chronic low back pain. BMC Musculoskelet Disord. 2023;24(1):877.https://doi.org/10.1186/s12891-023-07019-z
9. Leone CM, Lenoir C, van den Broeke EN. Assessing signs of central sensitization: A critical review of physiological measures in experimentally induced secondary hyperalgesia. Eur J Pain. 2025;29(3):e4733.https://doi.org/10.1002/ejp.4733
10. Till SR, As-Sanie S, Schrepf A. Psychology of Chronic Pelvic Pain: Prevalence, Neurobiological Vulnerabilities, and Treatment. Clin Obstet Gynecol. 2019;62(1):22-36.https://doi.org/10.1097/grf.0000000000000412
11. Johnson S, Bradshaw A, Bresnahan R, Evans E, Herron K, Hapangama DK. Biopsychosocial Approaches for the Management of Female Chronic Pelvic Pain: A Systematic Review. Bjog. 2025;132(3):266-77.https://doi.org/10.1111/1471-0528.17987
12. Ryan A, Healey M, Cheng C, Dior U, Reddington C. Central sensitisation in pelvic pain: A cohort study. Aust N Z J Obstet Gynaecol. 2022;62(6):868-74.https://doi.org/10.1111/ajo.13596
13. Carroll L, Sullivan CO, Doody C, Perrotta C, Fullen BM. Pelvic organ prolapse: Women's experiences of Accessing Care & Recommendations for improvement. BMC Womens Health. 2023;23(1):672.https://doi.org/10.1186/s12905-023-02832-z
14. Carroll L, C OS, Doody C, Perrotta C, Fullen B. Pelvic organ prolapse: The lived experience. PLoS One. 2022;17(11):e0276788.https://doi.org/10.1371/journal.pone.0276788
15. Persu C, Chapple CR, Cauni V, Gutue S, Geavlete P. Pelvic Organ Prolapse Quantification System (POP-Q) - a new era in pelvic prolapse staging. J Med Life. 2011;4(1):75-81.https://doi.org/
16. Practice Bulletin No. 176: Pelvic Organ Prolapse. Obstet Gynecol. 2017;129(4):e56-e72.https://doi.org/10.1097/aog.0000000000002016
17. Starzec-Proserpio M, Frawley H, Bø K, Morin M. Effectiveness of nonpharmacological conservative therapies for chronic pelvic pain in women: a systematic review and meta-analysis. Am J Obstet Gynecol. 2025;232(1):42-71.https://doi.org/10.1016/j.ajog.2024.08.006
18. Schulten SFM, Claas-Quax MJ, Weemhoff M, van Eijndhoven HW, van Leijsen SA, Vergeldt TF, et al. Risk

factors for primary pelvic organ prolapse and prolapse recurrence: an updated systematic review and meta-analysis. Am J Obstet Gynecol. 2022;227(2):192-208.https://doi.org/10.1016/j.ajog.2022.04.046

19. Sandrieser L, Heine J, Bekos C, Perricos-Hess A, Wenzl R, Husslein H, et al. Evaluating the Correlation between Myofascial Pelvic Pain and Female Sexual Function: A Prospective Pilot Study. J Clin Med. 2024;13(16).https://doi.org/10.3390/jcm13164604
20. Raja SN, Sivanesan E, Guan Y. Central Sensitization, N-methyl-D-aspartate Receptors, and Human Experimental Pain Models: Bridging the Gap between Target Discovery and Drug Development. Anesthesiology. 2019;131(2):233-5.https://doi.org/10.1097/aln.0000000000002808
21. Wu H, Xie L, Chen Q, Xu F, Dai A, Ma X, et al. Activation of GABAergic neurons in the dorsal raphe nucleus alleviates hyperalgesia induced by ovarian hormone withdrawal. PAIN. 2025;166(4):759-72.https://doi.org/10.1097/j.pain.0000000000003362
22. Jayathilake NJ, Phan TT, Kim J, Lee KP, Park JM. Modulating neuroplasticity for chronic pain relief: noninvasive neuromodulation as a promising approach. Exp Mol Med. 2025;57(3):501-14.https://doi.org/10.1038/s12276-025-01409-0
23. Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain. 2015;156 Suppl 1:S24-s31.https://doi.org/10.1097/01.j.pain.0000460343.46847.58
24. Weaver KR, Griffioen MA, Klinedinst NJ, Galik E, Duarte AC, Colloca L, et al. Quantitative Sensory Testing Across Chronic Pain Conditions and Use in Special Populations. Front Pain Res (Lausanne). 2021;2:779068.https://doi.org/10.3389/fpain.2021.779068
25. Klotz SGR, Kolbe C, Rueß M, Brünahl CA. The role of psychosocial factors in the interprofessional management of women with chronic pelvic pain: A systematic review. Acta Obstet Gynecol Scand. 2024;103(2):199-209.https://doi.org/10.1111/aogs.14708
26. Vandyken B, Keizer A, Vandyken C, Macedo LG, Kuspinar A, Dufour S. Pelvic floor muscle tenderness on digital palpation among women: convergent validity with central sensitization. Braz J Phys Ther. 2021;25(3):256-61.https://doi.org/10.1016/j.bjpt.2020.05.013
27. Kaya S, Hermans L, Willems T, Roussel N, Meeus M. Central sensitization in urogynecological chronic pelvic pain: a systematic literature review. Pain Physician. 2013;16(4):291-308.https://doi.org/
28. Dewitte M, Meulders A. Fear Learning in Genital Pain: Toward a Biopsychosocial, Ecologically Valid Research and Treatment Model. J Sex Res. 2023;60(6):768-85.https://doi.org/10.1080/00224499.2022.2164242
29. O'Laughlin DJ, Strelow B, Fellows N, Kelsey E, Peters S, Stevens J, et al. Addressing Anxiety and Fear during the Female Pelvic Examination. J Prim Care Community Health. 2021;12:2150132721992195.https://doi.org/10.1177/2150132721992195
30. Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain. 2005;119(1-3):5-15.https://doi.org/10.1016/j.pain.2005.06.031
31. Skljarevski V, Zhang S, Desaiah D, Alaka KJ, Palacios S, Miazgowski T, et al. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. J Pain. 2010;11(12):1282-90.https://doi.org/10.1016/j.jpain.2010.03.002
32. Finnerup NB, Gottrup H, Jensen TS. Anticonvulsants in central pain. Expert Opin Pharmacother. 2002;3(10):1411-20.https://doi.org/10.1517/14656566.3.10.1411
33. Guy S, Mehta S, Leff L, Teasell R, Loh E. Anticonvulsant medication use for the management of pain following spinal cord injury: systematic review and effectiveness analysis. Spinal Cord. 2014;52(2):89-96.https://doi.org/10.1038/sc.2013.146
34. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and Central Sensitization in Chronic and Widespread Pain. Anesthesiology. 2018;129(2):343-66.https://doi.org/10.1097/aln.0000000000002130
35. Valentine LN, Deimling TA. Opioids and Alternatives in Female Chronic Pelvic Pain. Semin Reprod Med. 2018;36(2):164-72.https://doi.org/10.1055/s-0038-1676102
36. Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. Am Psychol. 2014;69(2):153-66.https://doi.org/10.1037/a0035747
37. Bazzari AH, Bazzari FH. Advances in targeting central sensitization and brain plasticity in chronic pain. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2022;58(1):38.https://doi.org/10.1186/s41983-022-00472-y
38. Giordani G, De Angelis S, Parisi AI, D'Amico A C, Di Re M, Liumbruno C, et al. Manual Physiotherapy

Combined with Pelvic Floor Training in Women Suffering from Stress Urinary Incontinence and Chronic Nonspecific Low Back Pain: A Preliminary Study. Healthcare (Basel). 2022;10(10).https://doi.org/10.3390/healthcare10102031

39. Vieira GF, Saltiel F, Miranda-Gazzola APG, Kirkwood RN, Figueiredo EM. Pelvic floor muscle function in women with and without urinary incontinence: are strength and endurance the only relevant functions? a cross-sectional study. Physiotherapy. 2020;109:85-93.https://doi.org/10.1016/j.physio.2019.12.006
40. Chen Q, Zhang W, Sadana N, Chen X. Estrogen receptors in pain modulation: cellular signaling. Biology of Sex Differences. 2021;12(1):22.https://doi.org/10.1186/s13293-021-00364-5
41. Vinik AI, Tuchman M, Safirstein B, Corder C, Kirby L, Wilks K, et al. Lamotrigine for treatment of pain associated with diabetic neuropathy: results of two randomized, double-blind, placebo-controlled studies. Pain. 2007;128(1-2):169-79.https://doi.org/10.1016/j.pain.2006.09.040

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