Approach to Diagnosis and Management of Chronic Pelvic Pain in Women

Incorporating Chronic Overlapping Pain Conditions in Assessment and Management

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KEYWORDS

• Endometriosis • Vulvodynia • Pelvic myofascial pain • Central sensitization

KEY POINTS

- Half of the patients with chronic pelvic pain (CPP) have nongynecologic conditions contributing to pain symptoms.
- Patients with gynecologic pain conditions, such as endometriosis and vulvodynia, may be more vulnerable to the development of additional chronic overlapping pain conditions (COPCs).
- Pelvic myofascial pain should be considered in patients who suffer from gynecologic or pelvic COPCs, including endometriosis, vulvodynia, interstitial cystitis/bladder pain syndrome, or irritable bowel syndrome.
- Patients and clinicians should be aware that patients with multiple COPCs and higher degrees of central sensitization may not experience as robust an improvement with peripheral strategies alone.

INTRODUCTION

At least 15% to 20% of women suffer from chronic pelvic pain, which is defined as pain occurring in the abdomen or pelvis for at least 14 days per month and is severe enough to cause functional limitations or prompt medical care.[1] This condition has a profound impact on physical health, emotional well-being, and ability to function

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across family, social, and professional roles. Chronic pelvic pain is notoriously challenging to manage, frustrating patients and clinicians alike.

One of the reasons that chronic pelvic pain is so difficult to treat is that it is both multifactorial in etiology and highly heterogeneous in presentation. Although gynecologic etiologies, such as endometriosis, are commonly identified in patients with chronic pelvic pain, about half of patients with chronic pelvic pain have nongynecologic conditions contributing to their symptoms.[2] Patients with chronic pelvic pain very frequently suffer from other nonpelvic pain conditions, particularly those that comprise the chronic overlapping pain conditions (COPCs). COPCs are a set of chronic pain conditions that have a high probability of co-occurrence and appear to share common underlying mechanisms and risk factors. Two gynecologic pain conditions are included in the National Institutes of Health Pain Consortium list of COPCs: endometriosis and vulvodynia. But COPCs also include both pelvic (interstitial cystitis/bladder pain syndrome [IC/BPS] and irritable bowel syndrome [IBS]) and nonpelvic conditions (fibromyalgia, temporomandibular disorders [TMDs], migraine headache, chronic tension-type headache, chronic low back pain, and myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS]). The conditions that contribute to chronic pelvic pain symptoms in one person often differ greatly from those that contribute in another and can change in any given patient over their life course.

The presence of persistent pain, regardless of specific cause or location, can lead to increased sensitization of the central nervous system—in other words, predisposing patients to the development of additional chronic pain conditions.[3,4] Notably, patients with multiple chronic pain conditions often respond less robustly to treatments focused on individual conditions.[5–7] Therefore, it is essential to approach the management of chronic pelvic pain in a comprehensive manner, which includes identification of all conditions that contribute to pain symptoms and optimal management of each contributing condition.

The objectives of this review are to briefly review gynecologic, pelvic, and nonpelvic pain conditions that frequently occur in patients with chronic pelvic pain, to discuss how the presence of these overlapping conditions may influence treatment response, and to review some general management strategies for chronic pelvic pain, with particular attention to patients with co-occurring COPCs.

BRIEF REVIEW OF INDIVIDUAL CHRONIC OVERLAPPING PAIN CONDITIONS

In this section, we briefly review individual COPCs with the goal of familiarizing clinicians with these disorders so that they are more likely to recognize co-occurring conditions outside of their clinical expertise. We have organized this discussion by gynecologic, pelvic, and nonpelvic conditions. This is certainly not a comprehensive list of all potential conditions that may contribute to pain symptoms. For example, many patients with pelvic pain have significant contributions from pelvic myofascial pain, which we have discussed in detail in the Evaluation section below. Rather, this section is intended to serve as a brief introduction to this defined category of COPCs that are often underdiagnosed in patients with chronic pain, with the goal of facilitating screening and prompting referral to appropriate specialists.

Gynecologic Pain Conditions

Endometriosis

Endometriosis is a condition in which endometrial-like tissue is present outside the uterus. It is estimated to affect 10% of women of reproductive age.[8] Prevalence is much higher in women presenting with chronic pelvic pain (over 70%)[9] and in those

with infertility (21%–47%).[10] Endometriosis is most commonly found on the pelvic peritoneum, ovaries, tubes, but can also grow on other pelvic structures, such as colon, bladder, or appendix, and in more distant sites, such as diaphragm or pleural space. Endometriosis is classified according to stages using a variety of classification systems (eg, ASRM, Enzian, AAGL), all of which represent the anatomic disease burden identified at the time of surgical exploration. Although the higher stage corresponds to a higher probability of fertility-related issues and surgical complexity, it has little if any correlation with the degree of pain symptoms except dyspareunia.[11–13]

Symptoms of endometriosis are highly variable but may include dysmenorrhea, noncyclic pelvic pain, dyspareunia, dysuria, dyschezia, or infertility. Diagnosis of endometriosis is inherently challenging due to lack of reliable noninvasive diagnostic tools, heterogeneous symptom presentation, and the fact that the associated symptoms are nonspecific and can be seen in a variety of conditions. Although endometriosis may be suspected based on symptoms, diagnosis has traditionally required surgical confirmation. MRI is the most sensitive noninvasive diagnostic modality but is most effective in identifying advanced endometriosis with deep infiltrating lesions or endometriomas and typically does not identify superficial endometriosis lesions. Lack of sensitivity for superficial disease is notable, given high cost associated with MRI.

A recent study examining COPCs in a large health system administrative database evaluated co-occurrence of other COPCs diagnoses based on the index COPC diagnosis. Risk for co-occurrence of COPCs was substantially higher than risk for co-occurrence of several chronic non-pain conditions. For example, patients presenting with endometriosis were most likely to carry diagnoses of IC/BPS (odds ratio [OR] 18.62), vulvodynia (OR 15.56), and IBS (OR 5.05)[14] (**Table 1**).

Vulvodynia

Vulvodynia is defined as persistent vulvar pain present for at least 3 months without another identifiable etiology.[15] Prevalence is difficult to estimate as the diagnostic criteria have changed in recent years, but is thought to be present in at least 7% of women.[16] Vulvodynia can be spontaneous, provoked by contact, or mixed, and frequently contributes significantly to dyspareunia. Vulvodynia is a diagnosis of exclusion and it is essential to rule out infectious, inflammatory, malignant, and other etiologies before confirming the diagnosis.[15]

Nongynecologic Pelvic Pain Conditions

Interstitial cystitis/bladder pain syndrome

IC/BPS is a condition in which patients experience bladder discomfort, most commonly pain but may report primarily pressure or spasm symptoms. Typically, patients report increased discomfort with bladder filling, which improves after bladder emptying. Many patients experience urinary urgency and frequency, which is thought to be a coping technique to avoid the discomfort associated with bladder distention. This constellation of symptoms is frequently interpreted by patients and health care providers as a urinary tract infection, but typically patients will have an unremarkable urinalysis or urine culture.

Diagnosis of IC/BPS has evolved substantially over the last few decades. Current diagnostic criteria focus primarily on clinical symptoms. Additional testing, including urinalysis, urodynamics, cystoscopy, is used selectively to exclude other conditions that may have a similar presentation.[17] Selective cystoscopy is currently recommended to rule out other etiologies, such as malignancy or foreign body, in patients who are high-risk, or who are nonresponsive to conservative therapy.[18] Both the evolution

Table 1
Odd ratios for pairs of COPCs and three chronic non-COPCs with 95% confidence intervals

	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL	OR	LL	UL
	FM			**JBS**			**TMO**			**UCPPS**			**ENDO**		
FM				10.18	9.72	10.67	5.64	4.98	6.40	9.91	8.88	11.06	4.06	3.49	4.72
IBS	10.18	9.72	10.67				3.70	3.27	4.18	9.10	8.27	10.02	5.05	4.46	5.72
TMD	5.64	4.98	6.40	3.70	3.27	4.18				4.75	3.61	6.25	1.87	1.22	2.89
UCPPS	9.91	8.88	11.06	9.10	8.27	10.02	4.75	3.61	6.25				18.62	15.74	22.03
ENDO	4.06	3.49	4.72	5.05	4.46	5.72	1.87	1.22	2.89	18.62	15.74	22.03			
VVD	3.14	2.65	3.73	3.97	3.46	4.56	1.85	1.19	2.88	24.99	21.41	29.16	15.56	12.77	18.95
cLBP	5.29	5.09	5.51	2.29	2.20	2.39	1.24	1.10	1.40	2.34	2.11	2.60	2.30	2.04	2.60
cTTH	2.43	2.10	2.81	1.58	1.37	1.82	2.64	2.01	3.47	1.94	1.38	2.72	1.25	0.79	1.97
MHA	5.27	5.06	5.50	3.30	3.18	3.43	6.13	5.66	6.64	3.29	2.98	3.64	3.21	2.88	3.58
CFS	6.07	5.64	6.52	2.90	2.68	3.14	1.48	1.14	1.91	2.78	2.27	3.42	1.86	1.43	2.43
DN	2.60	2.27	2.98	1.66	1.45	1.90	N/A	N/A	N/A	0.86	0.52	1.40	N/A	N/A	N/A
COPD	3.14	2.94	3.36	1.78	1.66	1.90	0.89	0.71	1.12	1.05	0.84	1.31	0.54	0.37	0.80
CVH	2.20	1.88	2.57	1.48	1.27	1.72	0.56	0.31	1.02	1.19	0.76	1.84	N/A	N/A	N/A
	VVD			**cLBP**			**cTTH**			**MHA**			**ME/CFS**		
FM	3.14	2.65	3.73	5.29	5.09	5.51	2.43	2.10	2.81	5.27	5.05	5.50	6.07	5.64	6.52
IBS	3.97	3.46	4.56	2.29	2.20	2.39	1.58	1.37	1.82	3.30	3.18	3.43	2.90	2.68	3.14
TMO	1.85	1.19	2.88	1.24	1.10	1.40	2.64	2.01	3.47	6.13	5.66	6.64	1.48	1.14	1.91
UCPPS	24.99	21.41	29.16	2.34	2.11	2.60	1.94	1.38	2.72	3.29	2.98	3.64	2.78	2.27	3.42
ENDO	15.56	12.77	18.95	2.30	2.04	2.60	1.25	0.79	1.97	3.21	2.88	3.58	1.86	1.43	2.43
VVD				1.20	1.02	1.40	N/A	N/A	N/A	L63	1.42	1.87	1.19	0.85	1.66
cLBP	1.20	1.02	1.40				1.26	1.15	1.39	1.99	1.93	2.05	1.75	1.65	1.86
cTTH	N/A	N/A	N/A	1.26	1.15	1.39				4.27	3.98	4.58	1.82	1.51	2.20
MHA	1.63	1.42	1.87	1.99	1.93	2.05	4.27	3.98	4.58				2.67	2.52	2.83

ME/CFS	1.19	0.85	1.66	1.75	1.65	1.86	1.82	1.51	2.20	2.67	2.52	2.83			
DN	N/A	N/A	N/A	2.08	1.93	2.26	0.51	0.32	0.82	1.06	0.95	1.19	1.18	0.94	1.48
COPD	0.50	0.33	0.75	1.92	1.84	2.00	0.71	0.58	0.87	1.11	1.05	1.17	1.29	1.16	1.44
CVH	N/A	N/A	N/A	1.22	1.10	1.35	0.56	0.35	0.91	0.68	0.59	0.78	1.01	0.79	1.31
						0–1	1–3	2–5	5+						

Colors correspond to the strength of the relationship: light blue = moderate negative relationship; light yellow = moderate positive relationship; orange = strong positive relationship; and red = very strong positive relationship.

Abbreviations: cLBP, chronic low back pain; COPD, chronic obstructive pulmonary disease; cTTH, chronic tension-type headache; CVH, chronic viral hepatitis; DN, diabetic neuropathy; ENDO, endometriosis; FM, fibromyalgia; IBS, irritable bowel syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; MHA, migraine headache; TMD, temporomandibular disorder; UCPPS, urologic chronic pelvic pain syndrome; VVD, vulvodynia.

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of diagnostic criteria and the fact that IC/BPS is essentially a diagnosis of exclusion complicates estimates of prevalence. The most comprehensive assessments to date indicate 2% to 6% prevalence.[19] There is a very high prevalence of tenderness to palpation of bladder, urethra, and pelvic floor, indicating that pelvic myofascial pain is likely a significant contributor for many patients with this condition.

Irritable bowel syndrome

IBS is a functional gastrointestinal condition in which patients experience chronic abdominal pain and altered bowel habits. Abdominal pain symptoms may be intermittent or persistent, are often associated with bloating and increased gas production, and are frequently exacerbated with defecation. Patients may report diarrhea, constipation, or alternating stool consistency.[20] Prevalence of IBS is estimated to be around 11%, but fewer than half of patients have received a formal diagnosis by many estimates.[21] Diagnosis of IBS is primarily clinical, but evaluation should include at least a limited assessment to exclude other gastrointestinal conditions such as inflammatory bowel disease or structural lesions. For example, colonoscopy may be recommended if patients present with diarrhea and other alarming features, such as weight loss or onset of symptoms after age 50 years. Abdominal computed tomography scan may be recommended in patients who present with persistent constipation along with early satiety, pain, and bloating.

Nonpelvic Pain Conditions

Migraine headache

Migraine headache is a debilitating condition that is the third most prevalent condition in the world and the seventh leading cause of global burden of disease, affecting more than 10% of the world's population.[22] The 2 major subtypes are migraine without aura and migraine with aura. Migraine without aura is described as a moderate to severe unilateral pulsatile headache aggravated by physical activity and lasts 4 to 72 hours.[22] Many patients also experience nausea/vomiting, photophobia, and/or phonophobia. Migraine with aura is characterized by headache with preceding or accompanying transient focal neurologic symptoms. Typically, these episodes include visual or other sensory manifestations that are brief (minutes), unilateral, and fully reversible.[22]

Chronic tension-type headache

Chronic tension-type headache is defined as nonthrobbing headache present for at least 15 days per month for at least 6-month duration. Pain is much more likely to be present bilaterally compared to migraine but can occur unilaterally. Patients typically describe symptoms as pressure, squeezing, tightening, or "band-like." Tension-type headache is extremely common, estimated between 40% and 80% prevalence, but is episodic in the vast majority of cases.[23] Prevalence of chronic tension-type headache is estimated around 1% to 2%.[23] Migraine headache and chronic tension-type headache are not mutually exclusive and it is common for patients to suffer from both.

Temporomandibular disorders

TMDs are a group of musculoskeletal and neuromuscular disorders affecting the temporomandibular joint, muscles of mastication, and/or surrounding soft tissues.[24] Symptoms include dull, unilateral facial pain that is typically constant with intermittent exacerbations, often provoked by jaw motion. Pain often radiates toward the neck, ear, temporal, or periorbital areas. The prevalence of TMD is estimated to be at least 6% and is nearly twice as common among women than men.[25]

Chronic low back pain

Chronic low back pain is defined as back pain that continues for at least 12 weeks. Pain symptoms are variable, ranging from dull and aching to sharp and shooting. Most episodes of low back pain are self-limited and resolve within a few days to weeks. But approximately 20% of people with acute low back pain will develop more persistent symptoms. Although acute low back pain is extremely common, the prevalence of chronic low back pain is thought to be between 8% and 10%.[26] Etiology of low back pain is highly variable and may include myofascial, nerve, or bony contributions. Risk factors include increasing age, obesity, poor fitness level, and occupational factors, among others.

Fibromyalgia

Fibromyalgia is characterized by chronic widespread pain, fatigue, sleep disturbance, mood changes, and somatic symptoms.[27] Prevalence is estimated between 2% and 8%.[27] Central sensitization, or nociplastic pain, appears to play an important role in this condition.[27,28] Because the pain associated with fibromyalgia is widespread, it can be challenging to rule out other conditions, such as autoimmune disorders or osteoarthritis. Diagnosis is typically made by clinical history and physical examination, and imaging and laboratory studies are typically not useful except for ruling out other suspected diagnoses.[27] For example, pain limited to joints or pain associated with swelling of joints should prompt evaluation for an autoimmune condition such as rheumatoid arthritis. It is essential to note that this is not a disorder of the central nervous system alone and most patients with fibromyalgia have peripheral pain contributors, such as degenerative disc disease or osteoarthritis. However, patients with fibromyalgia typically perceive a greater degree of pain than would otherwise be anticipated based on the peripheral or nociceptive input.[29]

Myalgic encephalomyelitis/chronic fatigue syndrome

ME/CFS is characterized by at least 6-month duration of moderate to severe fatigue occurring at least 50% of the time, which is not relieved by rest, and is associated with symptoms such as postexertional malaise, sleep disturbance, cognitive dysfunction, pain, and orthostatic symptoms.[30] The prevalence is also variable due to multiple definitions of ME/CFS. Although the point prevalence of chronic fatigue seems to be at least 2% to 6%, the prevalence of patients meeting full diagnostic criteria for ME/CFS is likely less than 0.5%.[31,32]

RISK FACTORS FOR CHRONIC PAIN CONDITIONS

Studies examining risk factors for the development of chronic pain are abundant, and yet our understanding of the true underlying mechanisms that correspond to these risk factors remains limited. For example, many studies have demonstrated a relationship between chronic pain conditions and low socioeconomic status, lower educational attainment, unemployment, poor nutrition, limited physical activity, obesity, sleep disorders, mental health conditions, tobacco use, alcohol use, and opioid use.[33,34] But one can certainly understand the bidirectional relationship associated with these factors—experiencing chronic pain predisposes to the development of all of these issues. Similarly, it is challenging to disentangle the influence of age, race, sex, and history of abuse or trauma from factors such as health care provider unconscious bias or patient willingness to report pain symptoms, particularly relative to pain diagnoses that are associated more with functional than overtly anatomic etiologies.

With those caveats, we will focus primarily on 2 risk factors for chronic pain conditions: presence of another chronic pain condition and genetic vulnerability.

The presence of chronic pain in one location more than doubles the risk for development of new chronic pain in other, even distant, locations.[3,35] In fact, in longitudinal studies, the presence of pain in more than one region at baseline was the strongest predictor for development of chronic pain in addition locations.[4] The predisposition to development of additional chronic pain conditions likely relates to altered function in sensory and pain processing pathways in the central nervous system, which is discussed in more detail in the following.

Chronic pelvic pain conditions, such as endometriosis, and COPCs appear to have a significant genetic or heritable vulnerability. Risk for endometriosis increases 7 to 10 fold if present in a first-degree relative and several genetic variants have been identified that appear to be highly consistent with development of endometriosis as well as severity of disease stage.[8,36] There is also evidence of heritable risk for other COPCs based on twin studies. A large twin study of over 31,000 participants in Sweden indicated that a latent genetic risk factor was associated with all 4 of the COPCs under investigation (recurrent headache, IBS, ME/CFS, and chronic widespread pain).[37] Similarly, first-degree relatives of patients with a COPC appear to be more likely to have diverse pain manifestations, not only the COPC under investigation but these associations may also be due to shared environmental risk.[38,39]

COMMON MECHANISMS IN CHRONIC PAIN CONDITIONS

A growing body of evidence supports the concept that there are shared risk factors and pathophysiological mechanisms in the appearance of chronic pelvic pain and COPCs. Central sensitization, central pain amplification, and nociplastic pain are 3 terms with considerable overlap and all describe central nervous system abnormalities in sensory and pain processing pathways that ultimately augment and maintain chronic pain. A recent review covers these mechanisms in detail,[40] so we will only briefly summarize that literature here. Functional, structural, and chemical neuroimaging studies have demonstrated differences between patients with COPCs and healthy controls in resting-state connectivity, gray matter volume, and levels of excitatory neurotransmitter in sensory regions of the brain.[40] Similarly, many studies have indicated that those with COPCs display heightened sensitivity to experimental pain in areas of the body not considered symptomatic of the COPC—for example, a substantial number of patients with TMD are more sensitive to pain in areas distal from the face and jaw, suggesting a global rather than local pattern of pain sensitivity. This pattern has been noted across several chronic pelvic pain conditions and COPCs, including endometriosis, vulvodynia, IC/BPS, IBS, fibromyalgia, and headache.[41–46] Together, these findings suggest that central nervous system alterations with accompanying global hyperalgesia are generic, rather than condition-specific, features of COPCs. In addition, sensory sensitivity, both to bodily sensations and environmental stimuli, as well as constitutional symptoms such as sleep disturbances, fatigue, and cognitive dysfunction, are common across COPCs.[47,48]

A heightened inflammatory response to ex vivo stimulation of monocytes, t-cells, or whole blood by immunogenic substances is emerging as a marker of COPCs in several conditions. Animal models have consistently demonstrated a role for toll-like receptors (TLRs) in the spinal cord and brain toward pain sensitization and the transition from acute to chronic pain.[49] Studies in pain patients now suggest that the TLR responsiveness in circulating immune cells or whole blood show demonstrate a similar phenomenon. A heightened inflammatory response to lipopolysaccharide, a classic agonist of TLR-4, distinguishes female IC/BPS patients with additional COPCs from

those who have pelvic pain only and several other pain conditions including IBS and dysmenorrhea from healthy controls.[50–53]

These findings taken together provide substantial support for neurobiological substrates promoting generic risk for a COPC—the biological evidence for why COPCs do indeed overlap. Of course, additional condition-specific neurobiological risk factors remain an important area for investigation, but disease models that ignore shared biological pathways are necessarily limited to the subset of patients, more exception than rule, who have a single COPC.

Because COPCs share common mechanisms, many of the treatment strategies aimed at these mechanisms may be broadly applicable across many chronic pain conditions. We summarize strategies that target central sensitization in the following section. However, it is worth noting that most patients require multimodal treatment that addresses both the disease-specific or peripheral mechanisms in addition to central sensitization.

MANAGEMENT STRATEGIES FOR PATIENTS WITH CHRONIC PELVIC PAIN

Evaluation

A thoughtful and comprehensive history is essential for the evaluation of patients who present with chronic pelvic pain. Evaluation is typically specific to the suspected condition. A thoughtful physical examination and limited use of basic diagnostic or radiologic testing is typically adequate to diagnose many chronic pain conditions. But other conditions require more invasive testing to confirm diagnosis, such as surgical evaluation to confirm endometriosis. In patients with chronic pelvic pain, it is essential to evaluate for pelvic floor myofascial pain and co-occurring COPCs.

Pelvic myofascial pain

Pelvic myofascial pain is a condition in which pain originates from hypertonic or hypercontractile muscles. Myofascial pain is very common across many chronic pain conditions. Among women with chronic pelvic pain, 60% to 90% have musculoskeletal dysfunction contributing to their pain symptoms.[54,55] Although myofascial pain affects such a large proportion of people with pelvic pain, it is one of the most overlooked diagnoses in this population. Most people with conditions like endometriosis, vulvodynia, IBS, or IC/BPS have some component of myofascial pelvic pain. Pelvic myofascial pain is typically diagnosed based on pain with palpation of pelvic floor muscles, typically accessed through the vagina.

Symptoms of myofascial pain can vary depending on which muscles are malfunctioning and on the degree of spasticity. Pelvic myofascial pain is typically described as pelvic cramping, pressure, heaviness, aching, throbbing, soreness, or often as a "falling out sensation". Patients often report that pain occurs in the pelvis, vagina, vulva, bladder, or rectum, but frequently radiates to hips, buttocks, or legs. Pain often worsens throughout the day or with activities, such as standing or driving for long periods. Many people have exacerbations of pain related to menstrual periods, intercourse, bowel movements, urination, or having a full bladder, and pain can last for hours or days after an aggravating episode.

It is important to note that there is often overlap between symptoms of myofascial pelvic pain and other pelvic pain conditions, like endometriosis, vulvodynia, IBS, and bladder pain syndrome. Because the pelvic floor muscles are connected to and support the function of the pelvic organs, and because the pelvic floor muscles and pelvic organs share many sensory nerve pathways, it can be challenging to distinguish between pain originating in the pelvic organs versus the muscles based on symptoms alone.

Co-occurring chronic overlapping pain conditions

Primary care providers are typically more well versed in performing a thorough review of systems and obtaining a full picture of health history, whereas specialists often focus almost exclusively on the condition within their area of expertise. The risk of focused assessment is that a specialist may remain unaware of or may not uncover a patient's other COPCs, particularly given that many patients may not have the condition listed in their electronic medical record or have received a formal diagnosis. As discussed earlier, patients who have multiple COPCs or a significant degree of central sensitization often do not respond as robustly to peripherally focused treatments. So early identification of this risk factor can help the clinician and patient to have a more informed risk-benefit discussion regarding treatment options, particularly those associated with significant risk or recovery time such as surgical procedures.

Although it is not feasible or advisable for a subspecialist to manage conditions outside of their clinical expertise, simple screening measures can identify possible chronic pain conditions and features of central sensitization, which may help to facilitate referral to an appropriate specialist.

A fairly simple screening tool is the Complex Medical Symptoms Inventory (CMSI), which is a 41-item questionnaire designed to screen for cardinal symptoms of most COPCs.[56] Some chronic pain referral clinics opt to have patients complete more precise screening measures, such as Rome criteria for IBS or Pain, Urgency, and Frequency (PUF) score for IC/BPS. This is certainly a reasonable strategy if clinicians have the ability and time to interpret the screening tools accurately, particularly if there is a very high rate of overlap between specific conditions. However, clinicians should avoid giving a patient a definitive diagnosis outside of one's own clinical expertise, as many of these conditions are diagnoses of exclusion. Referral to an appropriate specialist ensures that the patient will have access to necessary evaluation to rule out more threatening etiologies.

As a reminder, the presence of a COPC does not absolve clinicians from performing appropriate evaluations for other anatomic or concerning etiologies. Many patients with COPCs have experienced delayed diagnoses of malignant, infectious, or inflammatory conditions because an appropriate evaluation was deferred due to suspicion that new or altered symptoms were likely attributed to their predisposition for the development of new COPCs.

Communication and Setting Expectations

Many patients with chronic pelvic pain or COPCs have received explicit or implicit messages from clinicians, friends, or family members that their pain was "all in their head." Many feel that their symptoms are not taken as seriously because these disorders are often not associated with significant anatomic abnormalities. Clear and empathetic communication is essential for developing therapeutic rapport. It is critical for clinicians to allow patients to tell their stories, to validate their symptoms and the impact on quality of life, and to be thoughtful and intentional when discussing the interaction between peripheral and central pain contributions.

Although every clinician and patient are hopeful that a particular treatment may result in complete resolution of pain, a focus on anticipated functional improvements may be more appropriate and realistic. Interestingly, many patients report that their goals are similar—they do not necessarily expect to be pain-free, but rather that they do not want pain to continue to dictate the degree to which they are able to participate in family, social, or professional roles. Patients and clinicians may obtain more insightful information about treatment response by asking the patient to identify a few personal functional goals and track progress relative to these rather than

continuing to focus exclusively on pain symptoms. Many patients identify improved sleep and fatigue, ability to play with their children, or fewer days of missed work as goals that are more reflective of their quality of life than a "pain score."

Treat Peripheral Contributions

Perception of any painful stimulus involves a complex interaction between peripheral sensory input and pain perception in both the peripheral and central nervous systems. In any given person with a chronic pain condition, there are varying degrees of peripheral input and central amplification contributing to the experience of pain and the likelihood of responding to a specific treatment. For example, endometriosis lesions can create inflammation that activates peripheral nerve receptors. The nerves carry this signal to the spinal cord and brain (central nervous system). The brain then categorizes the type of sensation, interprets location, and assesses intensity and bother associated with the sensation. The brain has a remarkable ability to "triage" or prioritize signals based on situational context. This triaging function is capable of amplifying or diminishing the brain's perception of pain.

This system typically works smoothly in situations involving acute pain, but chronic pain conditions are much more complex. Chronic pain may result from continued peripheral input, such as inflammation due to endometriosis lesions, from abnormal activation of nerves in the peripheral tissues or spinal cord, or from inappropriate triaging or amplification of pain perception in the central nervous system. Optimal treatment of any chronic pain condition must address both peripheral and central contributions.

Identifying all peripheral contributions is an essential step in developing a comprehensive treatment plan, highlighting again the importance of a thoughtful history and physical examination. For example, most patients with endometriosis, vulvodynia, IC/BPS, and IBS also have pelvic myofascial pain. If clinicians focus exclusively on endometriosis lesions or stool consistency without addressing myofascial contribution, patients are unlikely to experience a robust improvement in overall pain symptoms.

Several recent reviews summarize treatment strategies for individual gynecologic pelvic pain conditions,[57,58] so we will only summarize here. For patients with endometriosis, achievement of amenorrhea often results in significant improvement of pain. Surgical treatment of endometriosis can play an important role, but it is worth noting that identification or excision of endometriosis lesions does not rule out the possibility of other pain contributors, such as pelvic myofascial pain, and surgery alone does not represent a comprehensive evaluation.

Myofascial pain is highly prevalent across COPCs and many patients benefit from physical therapy as part of the treatment plan. In addition, physical therapists frequently incorporate pain education, cognitive behavioral strategies, and motivational interviewing in addition to manual therapy, which makes them an invaluable resource in the comprehensive treatment of both chronic pelvic pain and COPCs.[59]

As discussed previously, many patients with multiple COPCs unfortunately may experience less symptom improvement with individual treatment strategies, particularly those that are peripherally focused.[5–7] This certainly does not mean that patients with central sensitization should not have the opportunity to benefit from evidence-based peripheral treatments, such as medical or surgical treatment of endometriosis. But we would argue that clinicians have an ethical responsibility to include accurate information about anticipated outcomes in informed consent discussions, particularly when the patient is considering more invasive interventions such as surgery.

Treat Co-occurring Psychological Conditions

Prevalence of psychological conditions, such as depression and anxiety, is substantially increased in patients with chronic pain conditions compared with the general population, between 3- and 5-fold increased prevalence by most estimates.[60–64] Patients with concurrent chronic pain and psychological conditions experience more severe pain and worse quality of life compared with patients with chronic pain alone.[62,65]

Several theories have been proposed to explain the high rate of co-occurrence of chronic pain and psychological conditions, and a recent review addresses these in detail[66] so we will only summarize here. The relationship is almost certainly multifactorial, involving common genetic, inflammatory, and neurobiological vulnerabilities. We do believe that it is critical to highlight recent literature on the temporal relationship between these conditions. Several large prospective cohort studies indicate that pain predisposes to the development of mood disorders to a much greater degree than the reverse,[67,68] indicating that pain is not simply a manifestation of psychological distress.

Thoughtful presentation regarding the relationship between chronic pain and psychological conditions is essential in discussions with patients, as many may have had previous interactions within the medical community in which they felt that their pain was dismissed as psychological in origin and therefore may be quite hesitant to consider treatments targeting "mood disorders."

There are several validated tools that clinicians can use to screen for depression and anxiety. Some of the most widely used are PROMIS depression and PROMIS anxiety, which were developed in conjunction with the NIH as part of a large program to develop highly reliable measurement tools for a variety of patient-reported outcomes.[69] These screening tools are public availably, widely used in clinical practice or research applications, and have both long and short versions as well as Spanish-language versions. The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) are examples of other widely used, validated screening tools.

Focusing on the fact that we consider pain and psychological conditions to be distinct and separate diagnoses, clarifying our current understanding of the temporal relationship between the two, and highlighting the degree to which co-occurrence negatively impacts well-being and quality of life may help the patient to be more willing to consider treatment. This is likely to be much better received once a clinician has developed rapport and made substantive proposals to address peripheral pain contributions.

Finally, management of psychological conditions is best performed by a clinician who has experience in managing these medications and who can follow patients closely to make appropriate medication adjustments. Developing relationships with local psychiatric providers or primary care providers can help to facilitate timely and appropriate treatment.

Treat Central Sensitization

There is increasing recognition of the role that central sensitization plays in many chronic pain conditions, but much work remains in terms of screening for individual patients and in developing effective management strategies.

One of the most basic yet instructive screening tools is the American College of Rheumatology (ACR) 2011 Fibromyalgia Survey Score.[70] This self-report screening tool includes 2 components: the widespread pain index, which is the sum of total number of painful areas on a body map (0–19 points), and the symptom severity index, which asks about related symptoms such as fatigue, sleep dysfunction, or cognitive

symptoms (0–12 points). A score of ≥13 is diagnostic of fibromyalgia. However, the tool is frequently used as a continuous scale (0–31 points) that corresponds to the degree of central sensitization or nociplastic pain.[71] This measure is well validated for this purpose, has demonstrated excellent reliability, is highly predictive of pain and disability, and strongly corresponds to findings of central sensitization on functional neuroimaging.

Various pharmacologic and nonpharmacologic interventions have been evaluated to manage central sensitization, often with modest or conflicting results. Much of the difficulty is related to substantial heterogeneity among the conditions in which central sensitization contributes significantly. Furthermore, there is substantial heterogeneity with regard to the balance of peripheral and central contributions between individual patients with the same condition. Many chronic pain researchers and clinicians have endorsed a move to develop personalized treatment strategies, in which characteristics of an individual patient help clinicians predict which management strategies are likely to yield the greatest benefit, as opposed to relying on the current "trial and error" method.

Current best practices include using a multimodal approach that combines nonpharmacologic and pharmacologic strategies. Much of the available data for these strategies focus on specific COPCs, but we will focus primarily on strategies that have been used for chronic pelvic pain or are widely applicable for COPCs (**Table 2**).

Nonpharmacologic strategies

Exercise interventions have been evaluated across a multitude of chronic pain conditions and demonstrate improvements in pain, mood, sleep quality, and physical function.[72–74] Mechanism of action is unknown, but proposed theories include

Table 2
Managing central sensitization

Management Strategy	Clinical Pearls
Multimodal approach is key	Address peripheral contributors and co-occurring psychological conditions
Nonpharmacologic options	
Exercise and physical activity	"Start low, go slow" Yoga, aerobic, resistance
Cognitive behavioral therapy	Focus on functional improvement and coping mechanisms
Acupuncture/Acupressure	Work with local physical therapists and primary care physicians to find reputable and experienced providers
Pharmacologic options	
Antidepressants (TCA, SNRI)	Presentation is key—focus on neurotransmitter function rather than mood symptoms
Cyclobenzaprine	Addresses the "chronic pain triad"—myofascial pain, poor sleep, and central sensitization
Gabapentinoids	Use most or all of daily dose at bedtime to reduce daytime sedation
Cannabinoids	Know regulations in your state CBD ± THC Oral has longer duration of benefit than inhaled Topical may be less beneficial

anti-inflammatory effects, improvements in muscle function, and improved pain tolerance with repeated exposure to low levels of exercise-related discomfort. Many forms of exercise have been studied, including aerobic, resistance, and yoga, and there does not seem to be a clear optimal form. It may be best to encourage the patient to begin with an activity that they enjoy rather than prescribing a particular type of "exercise program." It is recommended to counsel patients to "start low and go slow" in terms of intensity and duration in order to minimize risk for pain exacerbations that may occur with an abrupt increase in activity level.[27]

Cognitive behavioral therapy (CBT) is a form of goal-directed psychological therapy that aims to help patients understand how their thoughts and behaviors may be contributing to their environment or disorder and focuses on tools to help modify those thoughts and behaviors. Pain education is also an integral component of CBT. It is very common for patients to develop maladaptive pain avoidance behaviors when pain has been present for a long time, and CBT can be very beneficial in helping to develop more adaptive coping techniques. Notably, CBT appears to be beneficial even in patients without mood disorders, suggesting broad applicability in the management of chronic pain conditions.[75] CBT has been evaluated in a variety of chronic pain conditions and has been associated with improvement in pain, physical function, and mood symptoms.[76–79] Interestingly, CBT modulated connections in pain-processing regions of the brain on functional MRI in patients with endometriosis.[18,80] Careful presentation of this strategy is essential, as many patients with chronic pain conditions may be hesitant to consider "therapy" given prior experiences with pain being dismissed as psychological in origin. Focus instead on the degree to which chronic pain has impacted physical function, sleep, mood, and relationships, and emphasize the potential for the development of more adaptive coping skills to improve quality of life.

Acupuncture is a traditional Chinese medicine therapy that targets specific points along "meridians" or pathways that run through the body. Acupuncture uses very thin needles to target these points, whereas acupressure uses external manual application of pressure. In dysmenorrhea and endometriosis, acupuncture or acupressure were associated with improvements in pain, physical function, fatigue, and quality of life.[78,81–83] Although many of the available studies are low quality or have high risk for bias, this appears to be a low-risk option when performed by trained providers and many patients anecdotally report success.

Pharmacologic strategies

Several classes of antidepressants have been used for various chronic pain conditions, particularly tricyclic antidepressants (TCAs) and serotonin–norepinephrine reuptake inhibitors (SNRIs). Both of these classes are thought to decrease pain sensitivity by increasing availability of norepinephrine in the descending pain modulatory pathways. Much of the data for these medications come from fibromyalgia, where SNRIs have demonstrated significant improvement in pain and quality of life, typically with fairly minimal side effects.[84,85] TCAs are associated with less robust improvement and use is more often limited by bothersome side effects.[86] Again, thoughtful presentation is key when discussing this option with patients and it is important to emphasize the role of neurotransmitters in pain signaling and perception.

Cyclobenzaprine is a centrally acting muscle relaxant that is pharmacologically similar to TCAs. Mechanism of action is also thought to be primarily related to increasing central availability of norepinephrine. In patients with fibromyalgia, use was associated with improved pain, sleep, and fatigue.[87,88] Many patients report drowsiness, which may limit daytime use but can be beneficial for pain-related sleep dysfunction.

Gabapentinoids, such as gabapentin and pregabalin, are centrally acting calcium channel blockers. This class of medication was initially developed for antiepileptic indications but has been extensively used, frequently off-label, in neuropathic pain conditions. Mechanism of action is thought to be primarily related to decreased activity in the ascending pain pathways by decreasing available glutamate and substance P, but they also appear to have some membrane stabilization activity. In patients with fibromyalgia, gabapentinoids are associated with improved pain, sleep, fatigue, and anxiety.[89] However, efficacy in chronic pelvic pain appears to be limited.[90] There is increasing concern about abuse or misuse of gabapentinoids, both with regard to nontherapeutic use and to risk for overdose when used concurrently with opioids.[91]

Cannabinoids are being increasingly used by patients with chronic pain conditions, despite fairly limited evidence regarding efficacy or safety. Cannabinoids are compounds derived from the cannabis plant. Over one hundred cannabinoids have been identified, but the 2 primary compounds are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the cannabinoid associated with the classic psychoactive effects of cannabis, whereas CBD does not have psychoactive properties. Various cannabinoids have been studied in chronic pain conditions and demonstrate modest improvements in pain and sleep.[92,93] Side effects are variable but may include sedation, dry mouth, dry eye, nausea, and dizziness, and range from mild to moderate in most studies.[92,93] Despite limited data regarding efficacy, patients with chronic pain conditions are increasingly considering cannabinoids, particularly as more countries and localities have legalized medical and/or recreational use. More evidence-based data are needed regarding efficacy, dose, route, and safety considerations.

Optimal Approach

The obvious question that arises after reviewing the aforementioned information is whether there is an algorithm or a validated stepwise approach that can be used when caring for patients with multiple chronic pain contributors. Everyone agrees that the trial-and-error approach is inefficient, inadequate, and demoralizing for patients and providers alike, but unfortunately, there is not yet a simple system that is able to effectively direct clinicians toward a personalized treatment plan for an individual patient.

The typical practice at our chronic pelvic pain and endometriosis referral clinic is to conduct a broad assessment for all potential pain contributors, including endometriosis, pelvic myofascial pain, COPCs, psychological conditions, and central sensitization at the initial consultation visit. We attempt to assess the degree to which each of these factors is driving pain symptoms, primarily based on an individual patient's history, symptoms, and physical examination. We discuss strategies to manage specific contributors, focusing on the fact that most patients require a multimodal, comprehensive approach. We are careful to present realistic expectations for anticipated responses to specific treatments and use shared decision making to decide how to proceed. When patients have a high degree of central sensitization, we preferentially recommend nonpharmacologic therapies, but admittedly access to cognitive behavior therapy and acupuncture is limited because of insurance coverage and provider availability in rural or underserved areas. When we feel that pharmacologic therapy is necessary, we attempt to individualize recommendations based on symptoms and historical responses to other medications. Because pelvic myofascial pain and sleep dysfunction are so prevalent among patients with chronic pelvic pain, we often begin with cyclobenzaprine or other muscle relaxants to target these symptoms in addition to shifting neurotransmitter activity. In a patient who has a mood disorder in addition to central sensitization, we may work with their primary care provider to

initiate a trial of SNRI medication. An interdisciplinary approach is essential, as no single provider has adequate expertise to manage all these conditions alone. This comprehensive, multimodal, interdisciplinary approach has been described in the literature and was associated with significant improvement in pain and quality of life.[94]

SUMMARY

Recognition of co-occurring COPCs can help clinicians provide better counseling and more tailored treatment recommendations for patients with chronic pelvic pain. Peripheral pain contributions should certainly be addressed using evidence-based management strategies, but clinicians must acknowledge the increased probability that pain may not improve sufficiently with peripheral treatments alone. Patients with co-occurring COPCs may benefit from the addition of treatments aimed at central sensitization, including pharmacologic and nonpharmacologic strategies.

CLINICS CARE POINTS

- Evaluation of chronic pelvic pain should be comprehensive. Identification of one pain condition does not exclude the possibility of additional pain contributors.
- Consider pelvic myofascial pain and chronic overlapping pain conditions in your differential for patients with chronic pelvic pain.
- Empathetic communication and setting goals focused on functional improvements rather than pain resolution can improve patient satisfaction.
- Patients with multiple COPCs or central sensitization should have the opportunity to benefit from evidence-based peripheral treatments, such as medical or surgical treatment of endometriosis. But patients should be counseled that they are at higher risk for residual or recurrent pain, particularly when considering more invasive interventions such as surgery.
- Treating co-occurring psychological conditions can significantly improve the quality of life.
- Central sensitization is often present in patients with multiple COPCs. Multimodal management strategies that include nonpharmacologic and pharmacologic strategies can modify the impact of central sensitization and improve both pain and quality of life.

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