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ONLINE EXCLUSIVE

Limited evidence guides empiric Tx of female chronic pelvic pain

Treat patients based on experience and by applying options used for other chronic pain syndromes. Lifestyle modifications can help, but avoid opioids.

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PRACTICE RECOMMENDATIONS

› *Consider the levonorgestrel-releasing intrauterine device for relief of chronic pelvic pain (CPP) from endometriosis; it's been found to be more effective than expectant management.* (B)

› *Prescribe a trial of depot medroxyprogesterone acetate, which was more effective than placebo for CPP for as long as 9 months.* (B)

› *Use gabapentin—with or without amitriptyline—to provide greater relief of CPP than amitriptyline alone.* (B)

› *Recommend pelvic physical therapy for CPP; the pelvic pain score can be reduced in proportion to the number of sessions.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE 1 ▶

Lisa G, 31 years old, gravida 0, complains of severe dysmenorrhea that began when she discontinued an oral contraceptive (OC) one year ago. Prior to stopping the OC, she had been taking an OC without interruption since she was 28, during which time she continued to have moderate symptoms of dysmenorrhea. Before taking an OC, the patient had a trial of an etonogestrel implant, which was removed because of irregular bleeding, and depot medroxyprogesterone acetate (MPA) injection, which she discontinued because of associated weight gain and fatigue.

Ms. G is not sexually active and doesn't want to start a family at this time, but is interested in having a diagnosis. She has no other medical problems, no surgical history, and no history of sexually transmitted infection. She reports that her mother and sister had endometriosis, including pain that resolved after definitive treatment.

Ms. G reports menstrual cycles that are exquisitely painful and occur regularly (every 28 days for 4 or 5 days), with a moderate volume of bleeding that requires a regular-size tampon change every 4 to 6 hours. She reports crampy abdominal pain as 10, on a scale of one to 10; dyschezia (without hematochezia); and generalized achy abdominal pain that is continuous during menses. Pain is partially controlled by ibuprofen, 800 mg every 8 hours. Ms. G also describes gastrointestinal symptoms of bloating, constipation preceding her menstrual cycle, diarrhea during her menses, and occasionally nausea and vomiting with the severe pain.

On examination (which is not performed during menses), Ms. G appears well and is not in acute distress. Abdominal examination is benign. There is no tenderness to palpation or distension; bowel sounds are normal. Pelvic examination reveals mild tenderness upon palpation of a small and mobile uterus. Rectal examination is normal. She has no signs of hyperandrogenism (eg, male-pattern body hair, central obesity).

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Chronic pelvic pain affects as many as 15% of women of reproductive age in the United States annually.

CASE 2 ▶

Rhonda M, 42 years old, gravida 3, para 3003, reports continuous pelvic pain for 7 years that is exacerbated by defecation, intercourse, and insertion of a tampon. She has a low level of dull baseline pain (3, on scale of one to 10) that occasionally spikes up to sharp, knifelike pain (10 on the pain scale), which, she says, brings her to tears. Ms. M describes the pain as "deep inside," central in her pelvis, and radiating to the left and right, particularly during pain flares.

The patient's 3 children were born by spontaneous vaginal delivery; however, she recalls that her youngest son was born via a traumatic vaginal delivery 8 years ago (he "got stuck coming out," she reports). The only other component of Ms. M's medical history is an anxiety disorder, for which she takes citalopram. She has a family history of cervical cancer.

Ms. M's past diagnostic work-up for pelvic pain includes pelvic ultrasonography, endometrial biopsy, Pap smear, and diagnostic laparoscopy—all normal. She had a negative gastrointestinal work-up, including upper- and lower-tract endoscopy. Medical therapy, including opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), did not provide significant relief of pain.

Despite the negative work-up, Ms. M is still concerned that the pain might be related to cancer. With her family history of cervical cancer, she says that she does not want to "miss anything."

Ms. M is thin and appears anxious. The abdomen is mildly and diffusely tender to palpation with normal bowel sounds and no distension. Pelvic examination reveals some hyperesthesia upon single-digit palpation of the pelvic floor. Placement of the speculum is difficult because of discomfort.

How would you proceed with the care of these patients?

What is chronic pelvic pain? Why is management such a challenge?

Chronic pelvic pain (CPP) is defined as chronic or intermittent cyclic or noncyclic pelvic pain lasting longer than 6 months, localized to the pelvis, diminishing a woman's quality of life, and requiring medical intervention.[1] It's estimated that CPP affects as many as 15% of women of reproductive age in the United States each year, at a cost to the health care system of approximately $2 billion annually.[2,3]

CPP can result from abnormal pain responses from multiple body systems, including gynecologic conditions such as endometriosis. Notably, a nongynecologic cause is more often the major pain generator, without significant identifiable pathology (**TABLE 1**). Like all chronic pain disorders, CPP can also result in central sensitization of the nervous system, altering how pain is processed at the level of the pain matrix in the brain.[4]

This article reviews the limited evidence for treating CPP and offers recommendations for the primary care physician on providing symptomatic relief in the absence of diagnosed pathology (**TABLE 2**[5-13]).

Treatment

Analgesics

NSAIDs are frequently used as first-line treatment for any kind of pain, including CPP. There is some evidence of benefit from NSAIDs, compared to placebo, in cyclic CPP secondary to dysmenorrhea and endometriosis;[5,6] however, evidence of effectiveness in noncyclic CPP is absent. Because of the low cost and availability of NSAIDs, a trial is reasonable as a first-line intervention, particularly in CPP suspected to be endometriosis or of musculoskeletal origin. NSAIDs can cause adverse effects, including nausea, vomiting, headache, and drowsiness in 11% to 14% of women, although these agents are generally well-tolerated on a short-term basis.[5]

Opioids bind to opioid receptors in the central and peripheral nervous systems, resulting in an analgesic effect. Guidelines issued in 2016 by the Centers for Disease Control and Prevention recommend safer prescribing through careful evaluation of the risks and benefits of opioids for pain not caused by cancer and for palliation as part of end-of-life care.[14]

The risks of opioid use are well known in the medical community; they include tolerance, physical dependence, misuse, and

TABLE 1
System-based causes of chronic pelvic pain

Organ system	Disease
Gynecologic	Adenomyosis
	Adhesive disease
	Endometriosis
	Ovarian cyst
	Ovarian remnant
	Pelvic congestion/pelvic venous insufficiency
	Pelvic inflammatory disease
	Tubal pathology (hydrosalpinx, pyosalpinx)
	Uterine leiomyoma
Neurologic	Disc herniation
	Nerve entrapment/irritation/impingement
	Postherpetic neuralgia
	Visceral sensitivity
Gastrointestinal	Chronic appendicitis
	Inflammatory bowel disease
	Irritable bowel syndrome
Urologic	Bladder pain syndrome/interstitial cystitis
	Urethritis
Musculoskeletal	Abdominal wall myalgia
	Coccydynia
	Fibromyalgia
	Pelvic floor tension myalgia
	Sacroiliac joint dysfunction
	Symphysis pubis pain
Psychological	Anxiety
	Depression
	Posttraumatic stress disorder
	Psychosexual dysfunction
	Sexual abuse
	Somatization disorders

death, in addition to common adverse effects such as nausea and vomiting, itching, constipation, and fatigue.[14,15] Because of those risks and limited long-term benefit in nonmalignant pain disorders, opioid therapy for CPP should be avoided.[14] For patients already taking an opioid, discuss a strategy for weaning and, if possible, provide home naloxone therapy in the event of accidental overdose.[14]

Hormonal therapy

Hormonal therapies are the most common nonsurgical treatment of noncyclic CPP, with or without a definitive diagnosis of endometriosis, in reproductive-age women with CPP.

Combined OCs, despite a lack of quality evidence, are frequently the first hormonal treatment tried in both cyclic and noncyclic

NSAIDs have inconclusive benefit over placebo in chronic pelvic pain secondary to endometriosis.

CPP. A low-dosage OC may decrease cyclic pain in endometriosis, although it can increase irregular bleeding and nausea.[16] As many as 53% of women with CPP reported having undergone a trial of an OC for endometriosis, despite the absence of consistent evidence showing effectiveness in CPP.[17]

Depot MPA, in trials, decreased pain more than placebo. It can be tried as a treatment, but its use is often limited because of adverse effects, such as weight gain and bloating.[8]

A trial of a levonorgestrel-releasing intrauterine device (LNG-IUD) is supported by moderate-quality evidence for women whose CPP is thought to be a symptom of endometriosis or to have another uterine origin.[7]

Gonadotropin-releasing hormone agonists, such as depot leuprolide and goserelin acetate implant, may be considered in a woman with a diagnosis of endometriosis whose pelvic pain is not alleviated by MPA or an LNG-IUD.[9]

Opioid therapy should be avoided in chronic pelvic pain because of significant risks presented by these agents and their limited long-term benefit in non-malignant pain disorders.

Nonhormonal therapies

CPP shares pain mechanisms with other pain syndromes, such as neuropathic pain. Antineuropathic medications, such as gabapentin and pregabalin, may, therefore, provide benefit. These medications also produce improvement in pain disorders of the musculoskeletal system, which may contribute to their analgesic effect.[18]

Gabapentin and amitriptyline have been studied in CPP; both were found successful in decreasing perceived pain. Of note, patients who received gabapentin, a gamma-aminobutyric acid analogue, with or without amitriptyline, had more pain relief than those treated with amitriptyline alone.[10] Adverse effects of these medications may limit their use (**TABLE 3**[19-25]).

Tricyclic antidepressants are well-supported, effective treatments for chronic pain through the central increase of norepinephrine. Beginning at a low dosage to diminish adverse effects (**TABLE 3**[19-25]) and increasing the dosage slowly to an effective level may increase adherence. A trial of at least 6 to 8 weeks, at a moderate dosage, is recommended before discontinuing the medication. Although amitriptyline has the most evidence for value in the management of CPP disorders,[10] second-generation tricyclic antidepressants nortriptyline and desipramine have also been used for pain control, and may be better tolerated.

Duloxetine and venlafaxine—serotonin–norepinephrine reuptake inhibitors—increase serotonin in addition to norepinephrine, which is believed to result in pain control. Although a systematic review of trials of duloxetine for chronic pain showed some improvement in diabetic peripheral neuropathy, fibromyalgia, chronic low back pain, and osteoarthritis, the review excluded CPP in its analysis.[26]

In our opinion, a selective neurotransmitter reuptake inhibitor can be attempted to diminish the central pain sensitization of CPP. As with all drugs that increase the availability of serotonin, serotonin syndrome is a rare risk. Additionally, when stopping duloxetine, a prolonged taper may be required.

Pelvic floor dysfunction therapy

Pelvic floor dysfunction of the musculature within the bony pelvis may contribute to, or cause, CPP. The pelvic floor musculature may be hypertonic or hypotonic, and trigger points may exist. Despite the frequency of pelvic floor dysfunction, detailed examination of the pelvic floor is not routinely performed during a pelvic exam.

Because of the high prevalence of pelvic floor dysfunction in women with CPP, evaluation of the pelvic floor muscles is warranted.[27] (A protocol for this evaluation is detailed in **TABLE 4**.) Pelvic dynamometry may indicate muscle spasm or chronic tension; palpation of the pelvic floor during the exam can also identify a pain generator.

Although it might be difficult to distinguish pelvic floor myofascial pain as the primary or secondary cause of pain, pelvic floor physical therapy may clarify the role of the pelvic floor response (depending on the patient's clinical exam and history). A low-quality retrospective case study on pelvic floor physical therapy reported significant improvement in pain that was proportional to the number of sessions completed.[11]

TABLE 2

Quality of evidence for interventions for chronic pelvic pain[5-13]

Intervention	Benefit	Quality of evidence	Study findings	Disadvantages
NSAIDs[5,6]	Unknown	No consistent evidence for chronic pelvic pain	NSAIDs are more effective than placebo for dysmenorrhea Inconsistent evidence for endometriosis Inconsistent evidence that any one type of NSAID is more effective than other types	NSAIDs present a greater risk of gastrointestinal and neurologic adverse effects than placebo
Combined oral contraceptives[7]	Unknown	No consistent evidence for chronic pelvic pain	N/A	None
Depot medroxyprogesterone acetate[8]	Yes	Moderate	More effective than placebo; 50% reduction in visual analogue pain scale after 9 months	Adverse effects include weight gain and bloating
Levonorgestrel-releasing intrauterine device[7]	Yes (for patients with a diagnosis of endometriosis)	Moderate	More effective than expectant management for pain relief	None
Gonadotropin-releasing hormone agonists[8,9]	Yes (for patients with a diagnosis of endometriosis)	Low	Depot leuprolide improved pelvic pain more than placebo at end of 12 weeks Goserelin acetate implant improved pelvic pain more than progesterone at 1 year	Adverse effects include vasomotor symptoms (hot flushes) and osteopenia (with long-term use) Therapy >6 months may require add-back estrogen
Antineuropathic agents[8,10]	Yes	Low	Gabapentin, amitriptyline, and the 2 agents in combination provide pain relief; gabapentin alone is most effective	Adverse effects include somnolence and weight gain
Pelvic floor therapy[11]	Yes	Low	In a retrospective study, pain score improved in proportion to the number of sessions; 63% of patients reported significant improvement or resolution	Need access to a trained physical therapist
Botulinum toxin A[12]	Yes	Low	In a comparison of injection of botulinum toxin A and saline injection, both cohorts had a reduction in pain score; the botulinum toxin A cohort more so, but not significantly	Need training to administer Rare risk of skeletal or respiratory muscle weakness
Psychological therapy[8,13]	No	Low	No difference in pain relief with somatocognitive therapy, psychotherapy, or an integrated approach (ie, somatic, psychological, dietary, environmental, and physical therapy) than with standard care or placebo	Studies are small and heterogeneous

N/A, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs.

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TABLE 3

Nonhormonal, nonanalgesic medications used for chronic pain syndromes[19-25]

Medication	Recommended dosing*	Adverse effects	Other considerations
Tricyclic antidepressants			
Amitriptyline	*Initial dosage*: 10-25 mg/d at bedtime *Titrate*: 10-25 mg/wk to a maximum dosage of 75-100 mg/d at bedtime[19]	Sedation, dry mouth, constipation, weight gain, tachycardia, hyperglycemia	Urinary retention
Nortriptyline	*Initial dosage*: 10 mg/d at bedtime *Titrate*: 10 mg/wk to a maximum dosage of 50-100 mg/d at bedtime[20]	Similar to amitriptyline at higher dosages	
Desipramine	*Initial dosage*: 25 mg/d *Titrate*: 10-25 mg/wk to a maximum dosage of 75-100 mg/d[21]	Similar to amitriptyline at higher dosages	
Serotonin–norepinephrine reuptake inhibitors			
Duloxetine	*Initial dosage*: 20 mg/d *Titrate*: 20 mg/wk to a maximum dosage of 60-90 mg/d[22]	Sedation, headache, dizziness, loss of libido	Take caution when co-administering with other serotonergic medications because of the risk of serotonin syndrome and inducement of mania in bipolar disorder; taper-off required
Venlafaxine	*Initial dosage*: 75 mg/d in 2 divided doses *Titrate*: 37.5 mg/wk to a maximum dosage of 150-225 mg/d in 2 divided doses[23]	Nausea, vomiting, diarrhea, weight gain, dry mouth, headache, fatigue, hyperhidrosis	
Gamma-aminobutyric acid analogues			
Gabapentin	*Initial dosage*: 100 mg/d at bedtime *Titrate*: 100 mg weekly to 300 mg/d at bedtime; then, increase by 100-300-mg doses, given in 2 or 3 divided doses, to a maximum dosage of 3600 mg/d[24]	Sedation, weight gain, headache, dizziness, blurred vision, lower-extremity edema	Taper-off required
Pregabalin	*Initial dosage*: 25 mg at bedtime *Titrate*: 25 mg bid; then, increase by 25 mg/d in 2 or 3 divided doses, to a maximum dosage of 600 mg/d[25]	Dizziness, somnolence, ataxia, asthenia, weight gain, difficulty with concentration or thinking	

*Dosing information in this column reflects: (1) the authors' experience; (2) referenced guidance from the US Food & Drug Administration (FDA) and other expert sources;[19-25] and (3) the authors' knowledge of these agents' potential adverse effects. "Maximum dosages" are within the limits of FDA recommendations.

Trigger-point injections and injections of botulinum toxin A have been used with reported improvement in the pelvic floor pain profile, and there is evidence to support the benefit of such injections in pelvic muscle dysfunction.[12]

Psychotherapy

Cognitive behavioral therapy (CBT) is well established as an option to manage a patient's response to pain, including teaching coping skills for a chronic pain disorder and pain flares. Evidence supports using CBT or mindfulness techniques over usual care in reducing the intensity of pain in chronic low back pain,[28] and may be helpful in CPP. Patients with CPP who received 10 treatments of Mensendieck somatocognitive therapy (a mind–body therapy technique popular in Eu-

TABLE 4

Protocol for a detailed pelvic examination in a woman reporting chronic pelvic pain

In the following order:
1. Perform an external pelvic evaluation.
2. Examine the vulvar vestibule and hymen by gently rolling a moistened cotton swab circularly.
3. Perform a single-digit examination of the pelvic floor muscles:
• Assess the general tone of the pelvic floor.
• Have the patient perform a Kegel exercise (ask her to gently squeeze the pelvic floor muscles, as if to stop the flow of urine midstream) so that you can evaluate her control of those muscles.
• Evaluate the tenderness and tonicity of the pelvic floor muscles by exerting pressure with a single index finger to the muscles listed below. With each palpation, have the patient describe whether she feels pain or pressure and, if she feels pain, whether she considers it mild, moderate, or severe. Evaluate: – **levator ani**, at the 5 o'clock and 7 o'clock positions, just beyond the hymen. – **internal obturator muscle**, identified by hooking the index finger around the pubic rami and placing your nondominant hand on the outside of the knee. Have the patient abduct her thigh into your hand, engaging the muscle vaginally; then, assess tenderness with your index finger that is placed vaginally. – **piriformis muscle**, identified deep in the vagina, near the apex of the cervix and lateral to the rectum on either side.
4. Evaluate the urethra and base of the bladder with an index finger.
5. Assess for pelvic pathology with a traditional speculum/bimanual examination.
6. Perform a rectovaginal examination when indicated.

rope) over 90 days, compared with standard treatment alone, demonstrated improvement in pain, motor function, and psychological distress that persisted 9 months after treatment.[13]

Lifestyle changes, complementary and alternative therapies

Although medical and nonpharmacotherapeutic treatments are often important in the management of CPP, lifestyle modifications should be addressed initially and throughout treatment. Specifically, in patients with chronic, nonmalignant pain, diet modifications, exercise, complementary and alternative therapies, and sleep improvement can improve the patient's ability to manage baseline pain and pain flares.

Diet modifications may relieve pain in some women with CPP. Although a systematic review in 2011 highlighted the lack of data available for the efficacy of dietary therapies for treating CPP, the authors did present data that a diet rich in antioxidants might alleviate pain sysmptoms.[29] Also, a gluten-free diet might reduce the symptoms of pain related to endometriosis and, thus, improve physical functioning, among other health domains.[30]

Exercise can be an important factor in the management of CPP, as with other chronic pain syndromes. In functional pain syndromes, the addition or maintenance of an exercise program has been shown to decrease the amount of pain medications required, improve depressive symptoms, increase energy, and decrease stress. Exercise also improves sleep quality and one's ability to cope with pain.[31]

Yoga provides a good balance of aerobic and muscle-building activity and, in the authors' experience, is tolerated by most women with CPP.

Acupuncture has limited evidence in the treatment of pelvic pain in women. Of the available studies, most are limited to pain related to endometriosis.[32]

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Exercise can have important benefits as part of a treatment plan for chronic pelvic pain.

Sleep hygiene may be an important consideration in managing CPP. Sleep disturbances are reported in more than 80% of women with CPP,[33] including excessive time in bed and frequent napping, resulting in daytime fatigue and feeling generally unrested. A recent meta-analysis reported mild-to-moderate immediate improvement in patients' pain after nonpharmacotherapeutic sleep interventions.[34] The National Sleep Foundation has produced a patient guide to assist in sleep hygiene.[35]

Devising a management strategy despite sparse evidence

Because the cause of noncyclic CPP may be multifactorial, and because the literature on the etiology of CPP is limited (and, when there is research, it is inconclusive or of poor quality[36]), there are few evidence-based recommendations for treating CPP. Given the paucity of quality evidence, physicians should treat patients empirically, based on their experience and their familiarity with the range of medical and nonpharmacotherapeutic options used to manage other chronic pain syndromes.

A recent meta-analysis reported mild-to-moderate immediate improvement in patients' pain after nonpharmacotherapeutic sleep interventions.

CASE 1 ▶

Ms. G's cyclic pelvic pain was present only during menses. The dyschezia, severe pain that began only after she discontinued a combined OC, aching pain, and severe menstrual cramps are, taken together, suggestive of endometriosis, despite a normal physical exam.

Medical and surgical options were reviewed with Ms. G. She elected to undergo diagnostic laparoscopy. Several extrauterine foci of endometrial tissue were noted and excised; an LNG-IUD was inserted. Her pain improved significantly after surgery.

CASE 2 ▶

Ms. M was found to have significant pain on single-digit examination of the pelvic floor muscles, indicating likely pelvic floor muscle dysfunction. Pelvic dynamometry revealed significant tightness and spasm in the pelvic floor muscles—specifically, the levator ani complex.

Ms. M was started on gabapentin to reduce baseline pain and was referred for pelvic floor physical therapy. She felt reassured that her risk of cancer was low, considering her negative work-up, and that cancer was not the cause of her pain. Her symptoms improved greatly with a regimen of medical and physical therapy, although she continues to experience pain flares. JFP

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