

Opioids: Overprescribing, alternatives, and clinical guidance

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Ob.Gyn. News

Overprescribing opioids leads to higher levels of consumption

Opioids are still often overprescribed after surgery, and the quantity of the prescription is associated with higher patient-reported consumption, according to a population-based study of surgery patients

Steve Cimino

Ryan Howard, MD, of the department of surgery at the University of Michigan, Ann Arbor, and his coauthors analyzed data from the Michigan Surgical Quality Collaborative and sampled 2,392 patients who underwent 1 of 12 common surgical procedures in Michigan between Jan. 1 and Sept. 30, 2017, and were prescribed opioids for pain. For all patients, the quantity of opioid prescribed—converted to oral morphine equivalents (OMEs) to adjust for varying potency—was considerably greater than the quantity actually consumed by the patient, wrote Dr. Howard and his colleagues in *JAMA Surgery*.

The study findings have troubling implications, the authors suggested. “Overprescribing was universally observed in this cohort, affecting each of the 12 procedures analyzed. This phenomenon was not limited to single, outlier institutions, but was widespread across many hospitals. This resulted in increased opioid consumption among patients who received larger prescriptions, as well as tens of thousands of leftover pills in 9 months that entered communities across the state of Michigan.”

The median amount prescribed was 150 OMEs, the equivalent of 30 pills of hydrocodone/acetaminophen, 5/325 mg. The median consumed, as reported by patients, was 45 OMEs, or 9 pills, meaning only 27% of the prescribed amount was used. Prescription size was also strongly associated with higher consumption; patients used an additional 0.53 OMEs (95% confidence interval, 0.40-0.65; $P < .001$), or 5.3 more pills, for every 10 extra pills prescribed. The larger the initial prescription, the more patients used, an association that persisted when the data were adjusted for procedure and patient-specific factors such as postoperative pain.

The study’s acknowledged limitations included an inability to estimate how many patients were contacted for patient-reported outcome collection, which obscures how representative this



sample may be of the patient population in general. There was also no data gathered regarding preoperative opioid use, a near certainty in this cohort given a 3% to 4% prevalence of chronic opioid use.

That said, the investigators noted that “intentionally keeping future recommendations liberal in quantity may ultimately aid with widespread adoption, especially for clinicians concerned that prescribing reductions may

lead to increased pain and calls for refills after surgery.” They commended local efforts already underway to combat this issue—including their own work at the University of Michigan, where evidence-based prescribing recommendations resulted in a 63% reduction in opioid prescription size without an increase in refills or pain—but reiterated that more needs to be done at a state level.

The authors offered a possible reason for the link between prescription size and patient consumption. “A plausible explanation for the association between prescription size and medication use is the anchoring and adjustment heuristic. This is a psychologic heuristic wherein a piece of information serves as an anchor on which adjustments are made to reach an estimation or decision. For example, obesity literature has shown that food intake increases with portion size. In this case, a larger amount of opioids may serve as a mental anchor by which patients estimate their analgesic needs.” ■

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Ob.Gyn. News

No change in postoperative pain with restrictive opioid protocol

“A promising strategy” to reduce opioid prescriptions

Bianca Nogrady

Opioid prescriptions after gynecologic surgery can be significantly reduced without impacting postoperative pain scores or complication rates, according to a paper published in *JAMA Network Open*.

A tertiary care comprehensive care center implemented an ultrarestrictive opioid prescription protocol (UROPP) then evaluated the outcomes in a case-control study involving 605 women undergoing gynecologic surgery, compared with 626 controls treated before implementation of the new protocol.

The ultrarestrictive protocol was prompted by frequent inquiries from patients who had used very little of their prescribed opioids after surgery and wanted to know what to do with the unused pills.

The new protocol involved a short preoperative counseling session about postoperative pain management. Following that, ambulatory surgery, minimally invasive surgery, or laparotomy patients were prescribed a 7-day supply of nonopioid pain relief. Laparotomy patients were also prescribed a 3-day supply of an oral opioid.

Any patients who required more than five opioid doses in the 24 hours before discharge were also prescribed a 3-day supply of opioid pain medication as needed, and all patients had the option of requesting an additional 3-day opioid refill.

Researchers saw no significant differences between the two groups in mean postoperative pain scores 2 weeks after surgery, and a similar number of patients in each group requested an opioid refill. There was also no significant difference in the number of postoperative complications between groups.

Implementation of the ultrarestrictive protocol was associated with significant declines in the mean number of opioid pills prescribed dropped from 31.7 to 3.5 in all surgical cases, from 43.6 to 12.1 in the laparotomy group, from 38.4 to 1.3 in the minimally invasive surgery group, and from 13.9 to 0.2 in patients who underwent ambulatory surgery.

“These data suggest that the implementation of a UROPP in a large surgical service is feasible and safe and was associated with a significantly decreased number of opioids dispensed during the perioperative period, particularly among opioid-naïve patients,” wrote Jaron Mark, MD, of the department of gynecologic oncology at Roswell Park Comprehensive Cancer Center, Buffalo, N.Y., and his coauthors. “The opioid-sparing effect was also marked and statistically significant in the laparotomy group, where most patients remained physically active and recovered well with no negative sequelae or elevated pain score after surgery.”

The researchers also noted that patients who were discharged home with an opioid prescription were more likely to call and request a refill within 30 days, compared with patients who did not receive opioids at discharge. ■

The study was supported by the Roswell Park Comprehensive Cancer Center, the National Cancer Institute and the Roswell Park Alliance Foundation. Two authors reported receiving fees and nonfinancial support from the private sector unrelated to the study.

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MASTER CLASS

Implementing enhanced recovery protocols for gynecologic surgery

Kirsten Sasaki, MD

“**E**nhanced Recovery After Surgery” (ERAS) practices and protocols have been increasingly refined and adopted for the field of gynecology, and there is hope among gynecologic surgeons—and some recent evidence—that, with the ERAS movement, we are improving patient recoveries and outcomes and minimizing the need for opioids. This applies not only to open surgeries but also to the minimally invasive procedures that already are prized for significant reductions in morbidity and length of stay. The overarching and guiding principle of ERAS is that any surgery—whether open or minimally invasive, major or minor—places stress on the body and is associated with risks and morbidity.

Enhanced recovery protocols are multidisciplinary, perioperative approaches designed to lessen the body’s stress response to surgery. The protocols and pathways offer us a menu of small changes that, in the aggregate, can lead to large and demonstrable benefits—especially when these small changes are chosen across the preoperative, intraoperative, and postoperative arenas and then standardized in one’s practice. Among the major components of ERAS practices and protocols are limiting preoperative fasting, employing multimodal analgesia, encouraging early ambulation and early postsurgical feeding, and creating culture shift that includes greater emphasis on patient expectations.

In our practice, we are incorporating ERAS practices not only in hopes of reducing the stress of all surgeries before, during, and after, but also with the goal of achieving a postoperative opioid-free hysterectomy, myomectomy, and extensive endometriosis surgery. (All of our advanced procedures are performed laparoscopically or robotically.)

Dr. Sasaki is an associate of the Advanced Gynecologic Surgery Institute. The author reported no disclosures relevant to this Master Class.

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Enhanced Recovery After Surgery protocols

Preoperative	Intraoperative	Postoperative
Patient counseling and expectations	Minimally invasive surgical approach	NSAIDs, acetaminophen, gabapentin
Avoid mechanical bowel preparation	Local anesthetic or long-acting local (liposomal bupivacaine)	Opioids only for breakthrough pain
Solids up to 6 hours prior to surgery	Keep patient warm	Regular diet within 24 hours
Clear liquids up to 2 hours prior to surgery	Intravenous fluid maintenance	Discontinue intravenous fluids within 24 hours
Consider acetaminophen, celecoxib, pregabalin, or gabapentin prior to surgery	Prophylaxis for nausea and vomiting (at least two classes of medications)	Ambulate within 24 hours
	Toradol (if appropriate)	

Frontline Medical News

Source: Adapted from ERAS Society recommendations

Over the past 7 or so years, we have adopted a multimodal approach to pain control that includes a bundle of preoperative analgesics—acetaminophen, pregabalin, and celecoxib (we call it “TLC” for Tylenol, Lyrica, and Celebrex)—and the use of liposomal bupivacaine in our robotic surgeries. We are now turning toward ERAS nutritional changes, most of which run counter to traditional paradigms for surgical care. And in other areas, such as dedicated preoperative counseling, we continue to refine and improve our practices.

Improved outcomes

The ERAS mindset notably intersected gynecology with the publication in 2016 of a two-part series of guidelines for gynecology/ oncology surgery from the ERAS Society. The 8-year-old society has its roots in a study group of European surgeons and others who decided to examine surgical practices and the concept of multimodal surgical care put forth in the 1990s by Henrik Kehlet, MD, PhD, then a professor at the University of Copenhagen.

The first set of recommendations addressed pre- and intra-operative care,¹ and the second set addressed postoperative

care.² Similar evidence-based recommendations were previously written for colonic resections, rectal and pelvic surgery, and other surgical specialties.

Most of the published outcomes of enhanced recovery protocols come from colorectal surgery. As noted in the ERAS Society gynecology/oncology guidelines, the benefits include an average reduction in length of stay of 2.5 days and a decrease in complications by as much as 50%.

There is growing evidence, however, that ERAS programs are also beneficial for patients undergoing laparoscopic surgery, and outcomes from gynecology—including minimally invasive surgery—are also being reported.

For instance, a retrospective case-control study of 55 consecutive gynecologic oncology patients treated at the University of California, San Francisco, with laparoscopic or robotic surgery and an enhanced recovery pathway—and 110 historical control patients matched on the basis of age and surgery type—found significant improvements in recovery time, decreased pain despite reduced opioid use, and overall lower hospital costs.³

The enhanced recovery pathway included patient education, multimodal antiemetics, multimodal analgesia, and balanced fluid administration. Early catheter removal, ambulation, and feeding were also components. Analgesia included routine preoperative gabapentin, diclofenac, and acetaminophen; routine postoperative gabapentin, NSAIDs, and acetaminophen; and transversus abdominis plane blocks in 32 of the ERAS patients.

ERAS patients were significantly more likely to be discharged on day 1 (91%, compared with 60% in the control group). Opioid use decreased by 30%, and pain scores on postoperative day 1 were significantly lower.

Another study looking at the effect of enhanced recovery implementation in gynecologic surgeries at the University of Virginia, Charlottesville, (gynecologic oncology, urogynecology, and general gynecology) similarly reported benefits for vaginal and minimally invasive procedures, as well as for open procedures.⁴

In the minimally invasive group, investigators compared 324 patients before ERAS implementation with 249 patients afterward and found that the median length of stay was unchanged (1 day). However, intraoperative and postoperative opioid consumption decreased significantly and—even though actual pain scores improved only slightly—patient satisfaction scores improved markedly among post-ERAS patients. Patients gave higher marks, for instance, to questions regarding pain control (“how well your pain was controlled”) and teamwork (“staff worked together to care for you”).

Reducing opioids

New opioid use that persists after a surgical procedure is a post-surgical complication that we all should be working to prevent. It has been estimated that 6% of surgical patients—even those who've had relatively minor surgical procedures—will become

long-term opioid users, developing a dependence on the drugs prescribed to them for postsurgical pain.

This was shown last year in a national study of insurance claims data from between 2013 and 2014; investigators identified adults without opioid use in the year prior to surgery (including hysterectomy) and found that 5.9% to 6.5% were filling opioid prescriptions 90-0 days after their surgical procedure. The incidence in a nonoperative control cohort was 0.4%.⁵ Notably, this prolonged use was greatest in patients with prior pain conditions, substance abuse, and mental health disorders—a finding that may have implications for the counseling we provide prior to surgery.

It's not clear what the optimal analgesic regimen is for minimally invasive or other gynecologic surgeries. What is clearly recommended, however, is that the approach be multifaceted. In our practice, we believe that the preoperative use of acetaminophen, pregabalin, and celecoxib plays an important role in reducing postoperative pain and opioid use. But we also have striven to create a practice-wide culture shift (throughout the operating and recovery rooms), for instance, that encourages using the least amounts of narcotics possible and using the shortest-acting formulations possible.

Transversus abdominis plane (TAP) blocks are also often part of ERAS protocols; they have been shown in at least two randomized controlled trials of abdominal hysterectomy to reduce intraoperative fentanyl requirements and to reduce immediate postoperative pain scores and postoperative morphine requirements.^{6,7}

More recently, liposomal bupivacaine, which is slowly released over several days, has gained traction as a substitute for standard bupivacaine and other agents in TAP blocks. In one recent retrospective study, abdominal incision infiltration with liposomal bupivacaine was associated with less opioid use (with no change in pain scores), compared with bupivacaine hydrochloride after laparotomy for gynecologic malignancies.⁸ It's significantly more expensive, however, making it likely that the formulation is being used more judiciously in minimally invasive gynecologic surgery than in open surgeries.

Because of costs, we currently are restricted to using liposomal bupivacaine in our robotic surgeries only. In our practice, the single 20 mL vial (266 mg of liposomal bupivacaine) is diluted with 20 mL of normal saline, but it can be further diluted without loss of efficacy. With a 16-gauge needle, the liposomal bupivacaine is distributed across the incisions (usually 20 mL in the umbilicus with a larger incision and 10 mL in each of the two lateral incisions). Patients are counseled that they may have more discomfort after 3 days, but by this point most are mobile and feeling relatively well with a combination of NSAIDs and acetaminophen.

With growing visibility of the problem of narcotic dependence in the United States, patients seem increasingly receptive and even eager to limit or avoid the use of opioids. Patients should be counseled that minimizing or avoiding opioids may also speed

recovery. Narcotics cause gut motility to slow down, which may hinder mobilization. Early mobilization (within 24 hours) is among the enhanced recovery elements that the ERAS Society guidelines say is “of particular value” for minimally invasive surgery, along with maintenance of normothermia and normovolemia with maintenance of adequate cardiac output.

Selecting steps

Our practice is also trying to reduce preoperative bowel preparation and preoperative fasting, both of which have been found to be stressful for the body without evidence of benefit. These practices can lead to insulin resistance and hyperglycemia, which are associated with increased morbidity and length of stay.

It is now recommended that clear fluids be allowed up to 2 hours before surgery and solids up to 6 hours before. Some health systems and practices also recommend presurgical carbohydrate loading (for example, 10 ounces of apple juice 2 hours before surgery) – another small change on the ERAS menu – to further reduce postoperative insulin resistance and help the body cope with its stress response to surgery.

Along with nutritional changes are also various measures aimed at optimizing the body’s functionality before surgery (“prehabilitation”), from walking 30 minutes a day to abstaining from alcohol for patients who drink heavily.

Throughout the country, enhanced recovery protocols are taking shape in gynecologic surgery. ERAS was featured in an

aptly titled panel session at the 2017 annual meeting of the American Association of Gynecologic Laparoscopists: “Outpatient Hysterectomy, ERAS, and Same-Day Discharge: The Next Big Thing in Gyn Surgery.” Others are applying ERAS to scheduled cesarean sections. And in our practice, I believe that if we continue making small changes, we will reach our goal of opioid-free recoveries and a better surgical experience for our patients. ■

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Postsurgical pain: Optimizing relief while minimizing use of opioids

Today, a 2-pronged strategy characterizes postoperative pain management: Offer analgesia with proven medical strategies, including multimodal approaches, and supported by patient education; and do this so that you curtail or avoid opioid analgesics

Mikio Nihira, MD, MPH, and Adam C. Steinberg, DO

CASE Managing pain associated with prolapse and SUI surgery

A 46-year-old woman (G4P4) described 3 years of worsening symptoms related to recurrent stage-3 palpable uterine prolapse. She had associated symptomatic stress urinary incontinence. She had been treated for uterine prolapse 5 years ago with vaginal hysterectomy, bilateral salpingectomy, and high uterosacral-ligament suspension.

After consultation, the patient elected to undergo laparoscopic sacral colpopexy, a mid-urethral sling, and possible anterior and posterior colporrhaphy. Appropriate discussion about the risks and benefits of mesh was provided preoperatively. The surgical team judged her to be highly motivated; she wanted same-day outpatient surgery so that she could go home and then return to work. She had excellent support at home.

How would you counsel this patient about expected postoperative pain? Which medications would you administer to her preoperatively and perioperatively? Which ones would you prescribe for her to manage pain postoperatively?



Although employed for several hundred years for pain management, opioids are highly addictive, have many adverse effects, and their use should be minimized or eliminated. All applicable categories of nonopioid alternatives for pain management and pain control strategies should be considered for surgical patients.

Adverse impact of prescription opioids in the United States

Although fewer than 5% of the world's population live in the United States, nearly 80% of the world's opioids are written for them.¹ In 2012, 259 million prescriptions were written for opioids in the United States—more than enough to give every American adult their own bottle of pills.² Sadly, drug overdose is now a leading cause of accidental death in the United States, with

52,404 lethal drug overdoses in 2015. A startling statistic is that prescription opioid abuse is driving this epidemic, with 20,101 overdose deaths related to prescription pain relievers and 12,990 overdose deaths related to heroin in 2015.³

It is likely that there are multiple reasons prescribing of opioids is epidemic. Surgical pain is a common indication for opioid prescriptions; fewer than half of patients who undergo surgery report adequate postoperative pain relief.⁴ Recognition of these deficits in pain management has inspired national campaigns to improve patients' experience with pain and aggressively address pain with drugs such as opioids.⁵

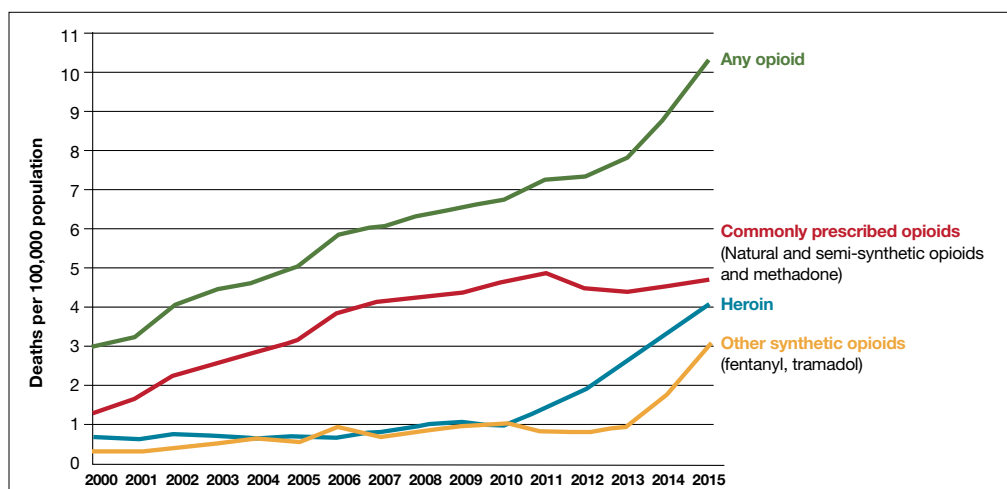
At the same time, marketing efforts by the pharmaceutical industry sought to reassure the medical community that patients would not become addicted to prescription opioid pain relievers if

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Dr. Nihira reported that he is a consultant to Pacira. Dr. Steinberg reported no financial relationships relevant to this article.

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FIGURE Overdose deaths involving opioids, United States, 2000–2015

Source: CDC/NCHS, National Vital Statistics System, Mortality, CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.

physical pain was the indication for such prescriptions. In response, health care providers began to prescribe opioids at a greater rate. As providers were encouraged to increase prescriptions, opioid medications began to be misused—and only then did it become clear that these medications are, in fact, highly addictive.⁹ Opioid abuse and overdose rates began to increase; in 2015, more than 33,000 Americans died because of an opioid overdose, including prescription opioids and heroin⁷ (FIGURE). In fact, although most people recognize the threat posed by illegal heroin, most of the 2 million who abused opioids in 2015 in the United States suffered from prescription abuse; only about a quarter, or about 600,000, abused heroin.⁸ In addition, more than 80% of people who abuse heroin initially abused prescription opioids.⁹

Multimodal approach to pain management

The goals of postsurgical pain treatment are to relieve suffering, optimize bodily functioning after surgery, limit length of the stay, and optimize patient satisfaction. Pain-control regimens should consider the specific surgical procedure and the patient's medical, psychological, and physical conditions; age; level of fear or anxiety; personal preference; and response to previous treatments.¹⁰

Optimally, postsurgical pain management starts well before the day of surgery. Employing such strategies as Enhanced Recovery after Surgery (ERAS) protocols does not necessarily mean providing the same care for every patient, every time. Rather, ERAS serves as a checklist to ensure that all applicable categories of pain medication and pain-control strategies are considered, selected, and dosed according to individual needs.¹¹ (See "Preoperative management of pain expectations.")

Opioids

Opioids have been employed to treat pain for 700 years.¹² They are powerful pain relievers because they target central mechanisms involved in the perception of pain. Regrettably, because of their central action, opioids have many adverse effects in addition to being highly addictive.

Nonopioid alternatives

Expert consensus, including recommendations of the World Health Organization,¹¹ favors using nonopioids as first-line medications to address surgical pain. Nonopioid analgesic options are acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and adjuvant medications. In addition, nonanalgesic medications such as sedatives, sleep aids, and muscle relaxants can relieve

postsurgical pain. Optimal use of these nonopioid medications can significantly reduce or eliminate the need for opioid medications to treat pain. Goals are to 1) reserve opioids for the most severe pain and 2) minimize the number of doses/pills of opioids required to control postsurgical pain.

Acetaminophen. At dosages of 325 to 1,000 mg orally every 4 to 6 hours, to a maximum dosage of 4,000 mg/d, acetaminophen can be used to treat mild pain and, in combination with other medications, moderate-to-severe pain. The drug also can be administered intravenously (IV), although use of the IV route is limited in many hospitals because of its significantly higher expense compared to the oral form.

The mechanism of action of acetaminophen is unique among pain relievers; it can therefore be used in combination with other pain relievers to more effectively treat pain with fewer concerns about medication-induced adverse effects or opioid overdose. However, keep in mind when considering combining analgesics,

Preoperative management of pain expectations

Ideally, before surgery, provide the patient with an opportunity to learn that:

- Her expectations about postsurgical pain should be realistic, and that freedom from pain is not realistic.
- Pain-reduction options should optimize her bodily function and mobility, reduce the degree to which pain interferes with activities, and relieve associated psychological stressors.
- Inherent in the pain management plan should be a goal of minimizing the risks of opioid misuse, abuse, and addiction—for the patient and for her family members and friends.

TABLE Adjuvant analgesic drugs^a

Medication	Uses	Starting dose	Dose range	Comments
Antidepressants (often use lower dosages to treat pain than to treat depression)				
Amitriptyline (Elavil) Nortriptyline (Pamelor) Desipramine (Norpramin)	Neuropathic pain	25 mg orally at bedtime (10 mg or less for elderly patients); titrate dose every few days to minimize side effects	75–150 mg orally at bedtime	Side effects include dry mouth, drowsiness, dizziness, constipation, orthostatic hypotension, urinary retention, confusion. Obtain baseline EKG for history of cardiac disease.
Selective serotonin and norepinephrine reuptake inhibitor (SSNRI) antidepressant				
Duloxetine (Cymbalta)	Diabetic peripheral neuropathy	30 mg	60 mg once daily sustained release	Should not use with MAOIs (Zyvox). Consider lower starting dose for patients for whom tolerability is a concern.
Antiepileptics				
Gabapentin (Neurontin)	Neuropathic pain	100–300 mg orally every 8 hours; increase by 100–300 mg every 3 days	300–3,600 mg/d	Adjust dose for renal dysfunction; can cause drowsiness
Pregabalin (Lyrica)	Diabetic peripheral neuropathy; postherpetic neuralgia; fibromyalgia	150 mg orally in 2–3 divided doses	150–600 mg/d (depending on indication)	Similar to gabapentin, often more rapid response than gabapentin; Schedule V controlled substance
Muscle relaxants				
Baclofen (Lioresal)	Muscle spasm	5 mg orally 3 times daily	80 mg orally in 24-hr divided doses	Caution in renal insufficiency
Tizanidine (Zanaflex)	Muscle spasm	4 mg daily—may be divided	36 mg/d	Gradually increase in 2–4 mg increments over 4 weeks; caution in elderly patients and those with renal insufficiency
Methocarbamol (Robaxin)	Muscle spasm	Up to 8 g daily in severe cases, decreasing as symptoms improve	4–4.5 g/d in 3–6 divided doses	Available IV 100 mg/mL or oral 750- or 500-mg tablets. IV should be given for maximum of 3 days only, but may be repeated 48 hours later.

^aMost commonly used drugs. Consideration should be given to comorbidities, hepatic and renal insufficiency, and age.

Abbreviations: EKG; electrocardiogram; MAOIs, monoamine oxidase inhibitors.

that acetaminophen is an active ingredient in hundreds of over-the-counter (OTC) and prescription formulations, and that a combination of more than one acetaminophen-containing product can create the risk of overdose.

Acetaminophen should be used with caution in patients with liver disease. That being said, multiple trials have documented safe use in normal body weight adults who do not have hepatic disease, at dosages as high as 4,000 mg over a 24-hour period.¹³

NSAIDs. A combination of an NSAID and acetaminophen has been documented to reduce the amount of opioid medications required to treat postsurgical pain. In most circumstances, especially for minor surgery, acetaminophen and NSAIDs can be administered just before surgery starts. This preoperative treatment, called “preventive analgesia” or “preemptive analgesia,”

has been demonstrated in multiple clinical trials to reduce postoperative pain.¹⁴

Adjuvant pain medications. Antidepressants, antiepileptic agents, and muscle relaxants—agents that have a primary indication for a condition (or conditions) other than pain and do not directly provide analgesia—have been used as adjuvant pain medications. When employed with traditional analgesics, they have been demonstrated to reduce postsurgical pain scores and the amount of opioids required. These medications need to be used cautiously because some are associated with serious sedation and vertigo (**TABLE**). Take caution when using adjuvant pain medications in patients older than 65 years; guidance on their use in older patients has been outlined by the American Geriatrics Society and other professional organizations.¹⁵

CASE Continued

The patient was given the expectation that the 11-mm left lower-quadrant port site would likely be the most bothersome site of pain—a rating of 4 or 5 on a visual analogue scale of 1 to 10, on postoperative day 1, while standing. The other 3 (5-mm) laparoscopic ports, she was told, would, typically, be less bothersome. The patient was educated regarding the role of analgesics and adjuvant medications and cautioned not to exceed 4,000 mg of acetaminophen in any 24-hour period. She was told that gabapentin may make her feel sedated or dizzy, or both; she was encouraged to hold this medication if she found these adverse effects bothersome or limiting.

The following multimodal pain management was established.

Preoperatively, the patient was given:

- Acetaminophen 1.5 g orally (as a liquid, 45 mL of a suspension of 500 mg/15 mL liquid), 2 to 3 hours preoperatively; the surgical suite did not stock IV acetaminophen.
- Gabapentin 600 mg orally, with a sip of water, the morning of surgery.
- Celecoxib 100 mg orally, with a sip of water, the morning of surgery.

Prescriptions for home postoperative pain management were provided preoperatively:

- OTC acetaminophen 1,000 mg (as two 500-mg tablets) taken as a scheduled dose every 8 hours for the first 48 hours postoperatively.
- Meloxicam 15 mg daily as the NSAID, taken as a scheduled dose once per day for the first 48 hours postoperatively, then as needed.
- Gabapentin 300 mg (in addition to the preoperative dose, above), taken as a scheduled dose every 8 hours for the first 48 hours postoperatively, then as needed.
- Oxycodone 5 mg (without acetaminophen) for breakthrough pain.

Intraoperatively:

- Meticulous attention was paid to patient positioning, to reduce the possibility of back and upper- and lower-extremity injury postoperatively.
- A corticosteroid (dexamethasone 8 mg IV) was administered to minimize postoperative nausea and vomiting and as an adjuvant medication for postoperative pain control.
- Careful attention was paid to limit residual CO₂ gas and intraoperative intra-abdominal pressures.
- All laparoscopic port sites were injected with 30 mL of 0.25% bupivacaine with epinephrine, extending to subcutaneous, fascial, and peritoneal layers.

Why a multimodal plan to treat pain?

Pain following laparoscopy has been associated with many variables, including patient positioning, port size and placement, amount of port manipulation, and gas retention. After a

A word about disposal of ‘excess’ opioids

The US Food and Drug Administration (FDA) recommends disposing of certain drugs through a take-back program or, if such a program is not readily available, by flushing them down a toilet or sink. In a recent study, investigators concluded that opioids on the FDA's so-called flush list include most opioids in clinical use—even if the entire supply prescribed is to be flushed down the drain. Conservative estimates of environmental degradation were employed in the study; the investigators' conclusion was that these drugs pose a “negligible” eco-toxicologic risk.¹

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laparoscopic surgical procedure, patients report pain in the abdomen, back, and shoulders.

Postsurgical pain has 3 components:

- **Shoulder pain**, thought to result from phrenic nerve irritation caused by lingering CO₂ in the abdominal cavity.
- **Visceral pain**, occurring secondary to stretching of the abdominal cavity.
- **Somatic pain**, caused by the surgical incision; of the 3 components to pain, somatic pain can have the least impact because laparoscopic incisions are small.

For our patient, prior to the incisions being made, she received local anesthesia intraoperatively to the laparoscopic port sites to include the subcutaneous, fascial, and peritoneal layers. Involving these layers allows for more of a block. An ultrasonography-guided transversus abdominis plane (TAP) block, if available, is highly effective at decreasing postoperative pain, but its efficacy is dependent on the anatomy and the skill of the physician (whether anesthesiologist, gynecologist, or surgeon) who is placing it.¹⁶

We used dexamethasone 8 mg IV, intraoperatively because this single dose has been shown to decrease the perception of pain postoperatively. Dexamethasone also has been shown to decrease consumption of oxycodone during the 24 hours after laparoscopic gynecologic surgery.¹⁷

CO₂ used to insufflate the patient's abdomen can take as long as 2 days to fully resorb, resulting in increased pain. This discomfort has been described as delayed; the patient might not notice it until she goes home. In a study, 70% of patients had shoulder discomfort following laparoscopy 24 hours after their procedure. For this reason, we employed several techniques to reduce this effect:

- We reduced the intra-abdominal pressure limit to 10 mm Hg (from 15 mm Hg) once dissection was complete.
- At the end of the procedure, careful attention was paid to removing as much intra-abdominal gas as possible, including placing the patient in the Trendelenburg position and having

Online resources for pain management

- Drug Disposal Information (US Department of Justice Drug Enforcement Administration) https://www.deadiversion.usdoj.gov/drug_disposal/index.html
- Surgical Pain Consortium <http://surgicalpainconsortium.org/>

the anesthesiologist induce a Valsalva maneuver. This action has been shown to significantly improve pain control compared to placebo intervention.¹⁹

- We used humidified CO₂, which has been demonstrated to reduce pain in laparoscopic surgery.²⁰
- Preemptively, we provided this patient with acetaminophen, celecoxib, and gabapentin, which have been demonstrated to be effective in gynecologic patients to decrease the need for postoperative opioids.²¹ Also, our patient received counseling, with specific expectations for what to expect following the surgical procedure.

CASE Resolved

Our patient did exceptionally well following surgery. She used only one of the oxycodone pills and did not require unplanned interventions. She took gabapentin, acetaminophen, and meloxicam at their scheduled doses for 2 days. She continued to use meloxicam for 4 more days for mild abdominal pain, then discontinued all medications. She flushed her 9 unused oxycodone pills down the toilet. (See “A word about disposal of ‘excess’ opioids” on page 12) The patient returned to her administrative duties at work 2 weeks after the procedure and reported that she was “very satisfied” with her surgical experience.

In conclusion

Postoperative pain is a complex entity that must be considered to require individualized strategies and, possibly, multiple interventions. Optimally, thorough education, including pain management options, is provided to the patient prior to surgery. Given the current state of opioid abuse in the United States, all gynecologic surgeons should be familiar with multimodal pain therapy and how to employ nonmedical techniques to reduce postsurgical pain without relying solely on opioids. ■

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Enhanced recovery after surgery for the patient with chronic pain

In comprehensive multimodal pain management, steps can be taken before, during, and after surgery to minimize opioid use and optimize pain control

Janelle K. Moulder, MD, MSCR, and Kathryn Paige Johnson, MD

CASE Chronic pelvic pain from endometriosis

A 40-year-old woman (G0) has a 20-year history of chronic pelvic pain. Stage III endometriosis is diagnosed on laparoscopic excision of endometriotic tissue. Postoperative pain symptoms include dysmenorrhea and deep dyspareunia, and the patient is feeling anxious. Physical examination reveals a retroverted uterus, right adnexal fullness and tenderness, and tenderness on palpation of the right levator ani and right obturator internus; rectovaginal examination findings are unremarkable. The patient, though now engaged in a pelvic floor physical therapy program, has yet to achieve the pain control she desires. After reviewing the treatment strategies for endometriosis with the patient, she elects definitive surgical management with minimally invasive hysterectomy and salpingo-oophorectomy.

What pre-, intra-, and postoperative pain management plan do you devise for this patient?

Chronic pelvic pain presents a unique clinical challenge, as pain typically is multifactorial, and several peripheral pain generators may be involved. Although surgery can be performed to manage anatomically based disease processes, it does not address pain from musculoskeletal or neuropathic sources. A complete medical history and a physical examination are of utmost importance in developing a comprehensive multimodal management plan that may include surgery as treatment for the pain.

The standard of care for surgery is a minimally invasive approach (vaginal, laparoscopic, or robot-assisted laparoscopic), as it causes the least amount of trauma. Benefits of minimally invasive surgery include shorter hospitalization and faster recovery, likely owing to improved perioperative pain control, decreased

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blood loss, and fewer infections. Although this approach minimizes surgical trauma and thereby helps decrease the surgical stress response, the patient experience can be optimized with use of enhanced recovery pathways (ERPs), a multimodal approach to perioperative care.

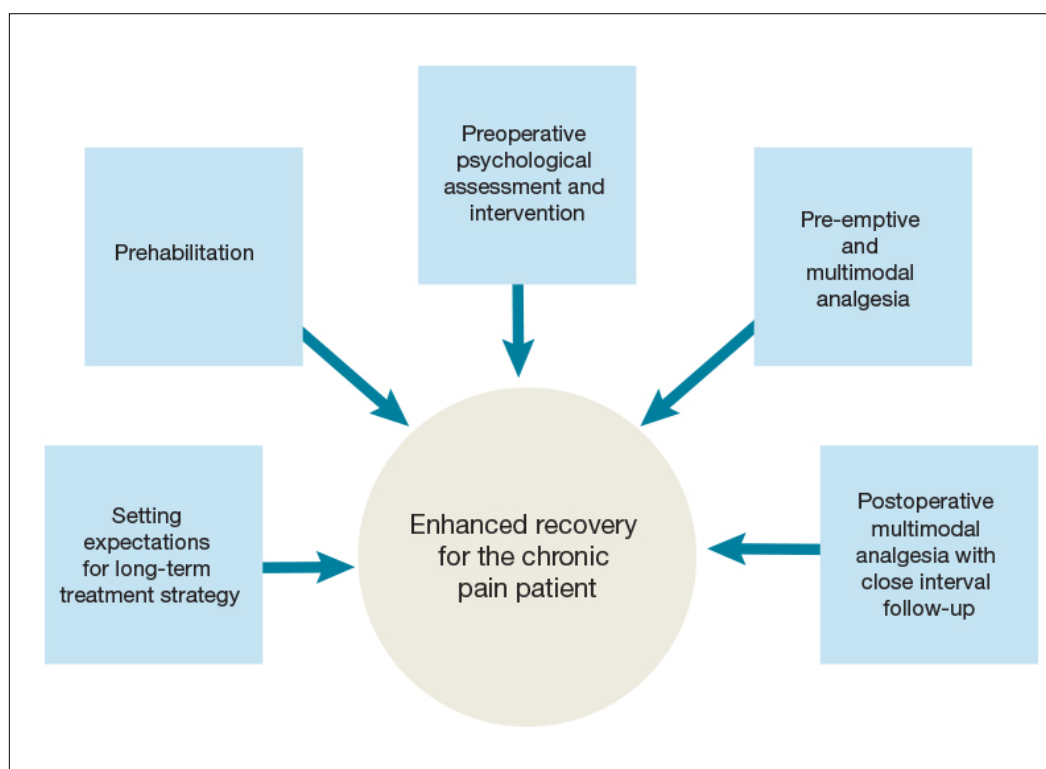
ERPs were initially proposed as a means of reducing the degree of surgical injury and the subsequent physiologic stress response.¹ This multimodal approach begins in the outpatient setting, includes preoperative and intraoperative modalities, and continues postoperatively. In patients with chronic pain, ERPs are even more important. Assigning “prehabilitation” and setting expectations for surgery goals are the first step in improving the patient experience. Intraoperative use of opioid-sparing anesthetics or regional anesthesia can improve recovery. After surgery, patients with chronic pain and/or opioid dependence receive medications on a schedule, along with short-interval follow-up. Ultimately, reducing acute postoperative pain may lower the risk of developing chronic pain.

In this article on patients with chronic pelvic pain, we highlight elements of ERPs within the framework of enhanced recovery after surgery. Many of the interventions proposed here also can be used to improve the surgical experience of patients without chronic pain.

Preadmission education, expectations, and optimization

Preoperative counseling for elective procedures generally occurs in the outpatient setting. Although discussion traditionally has covered the type of procedure and its associated risks, benefits, and alternatives, new guidelines suggest a more mindful and comprehensive approach is warranted. Individualized patient-centered education programs have a positive impact on the perioperative course, effecting reductions in preoperative anxiety, opioid requirements, and hospital length of stay.²

From a pain management perspective, the clinician can take some time during preoperative counseling to inform the patient about the pain to be expected from surgery, the ways the pain will be managed intraoperatively and postoperatively, and the multimodal strategies that will be used throughout the patient's stay² and that may allow for early discharge. Although preadmis-

FIGURE Enhanced recovery for the chronic pain patient

Strategies implemented preoperatively optimize the patient for surgery. Intraoperative and postoperative interventions continue a multimodal approach to pain management.

sion counseling still should address expectations for the surgery, it also presents an opportunity both to assess the patient's ability to cope with the physical and psychological stress of surgery and to offer the patient appropriate need-based interventions, such as prehabilitation and cognitive-behavioral therapy (CBT).

Prehabilitation is the process of increasing functional capacity before surgery in order to mitigate the stress of the surgery. Prehabilitation may involve aerobic exercise, strength training, or functional task training. The gynecologic surgery literature lacks prehabilitation data, but data in the colorectal literature support use of a prehabilitation program for patients having a scheduled colectomy, with improved postoperative recovery.³ Although the colectomy cohort predominantly included older men, the principle that guides program implementation is the same: improve recovery after the stress of abdominal surgery.

Indeed, a patient who opts for an elective surgery may have to wait several weeks before undergoing the procedure, and during this period behavioral interventions can take effect. With postoperative complications occurring more often in patients with reduced functional capacity, the data support using prehabilitation to decrease the incidence of postoperative complications, particularly among the most vulnerable patients.⁴ However, a

definitive recommendation on use of pelvic floor exercises as an adjunct to prehabilitation cannot be made.⁴

Successful prehabilitation takes at least 4 weeks and should be part of a multimodal program that addresses other behavioral risk factors that may negatively affect recovery.⁵ For example, current tobacco users have compromised pulmonary status and wound healing immediately after surgery, and use more opioids.⁶ Conversely, smoking cessation for as little as 4 weeks before surgery is associated with fewer complications.⁷ In addition, given that alcohol abuse may compromise the surgical stress response and increase the risk of opioid misuse, addressing alcohol abuse preoperatively may improve postoperative recovery.⁸

Treating mood disorders that coexist with chronic pain disorders is an important part of outpatient multimodal management—psychological intervention is a useful adjunct to prehabilitation

in reducing perioperative anxiety and improving postoperative functional capacity.⁹ For patients who have chronic pain and are undergoing surgery, it is important to address any anxiety, depression, or poor coping skills (eg, pain catastrophizing) to try to reduce the postoperative pain experience and decrease the risk of chronic postsurgical pain (CPSP).^{10,11}

Before surgery, patients with chronic pain syndromes should be evaluated for emotional distress and pain coping ability. When possible, they should be referred to a pain psychologist, who can initiate CBT and other interventions. In addition, pain coping skills can be developed or reinforced to address preoperative anxiety and pain catastrophizing. These interventions, which may include use of visual imagery, breathing exercises, and other relaxation techniques, are applicable to the management of postoperative anxiety as well.

Preoperative multimodal analgesia

Multimodal analgesia has several benefits. Simultaneous effects can be generated on multiple pain-related neurotransmitters, and a synergistic effect (eg, of acetaminophen and a nonsteroidal anti-inflammatory drug [NSAID]) can improve pain management.

In addition, small doses of multiple medications can be given, instead of a large dose of a single medication. Of course, this strategy must be modified in elderly and patients with impaired renal function, who are at high risk for polypharmacy.

Preoperative administration of 3 medications—a selective cyclooxygenase 2 (COX-2) inhibitor, acetaminophen, and a gabapentinoid—is increasingly accepted as part of multimodal analgesia. The selective COX-2 inhibitor targets inflammatory prostaglandins and has anti-inflammatory and analgesic effects; acetaminophen, an effective analgesic with an unclear mechanism of action, can reduce postoperative opioid consumption¹² and works synergistically with NSAIDs¹³; and the gabapentinoid gabapentin has an analgesic effect likely contributing to decreased movement-related pain and subsequent improved functional recovery (data are mixed on whether continuing gabapentin after surgery prevents CPSP).^{14–16}

Although serotonin and norepinephrine reuptake inhibitors (SNRIs) are commonly used in outpatient management of chronic pelvic pain, data suggest that their role in perioperative pain management is evolving. As SNRIs may reduce central nervous system (CNS) sensitization,¹⁷ their analgesic effect is thought to result from increased descending inhibitory tone in the CNS, which makes this class of medication ideal for patients with chronic neuropathic pain.¹⁵

Limited data also suggest a role for SNRIs in decreasing immediate postoperative pain and CPSP in high-risk patients. Studies of duloxetine use in the immediate perioperative period have found reduced postoperative acute pain and opioid use.^{18,19} In addition, a short course of low-dose (37.5 mg) venlafaxine both before and after surgery has demonstrated a reduction in postoperative opioid use and a reduction in movement-related pain 6 months after surgery.²⁰

Intraoperative management

The surgical and anesthesia teams share the goal of optimizing both pain control and postoperative recovery. Surgical team members, who want longer-acting anesthetics for infiltration of incision sites, discuss with the anesthesiologist the appropriateness of using peripheral nerve blocks or neuraxial anesthesia, given the patient's history and planned procedure. Anesthesia team members can improve anesthesia and minimize intraoperative opioid use through several methods, including total intravenous anesthesia,²¹ dexamethasone,²² ketorolac,²³ and intravenous ketamine. Ketamine, in particular, has a wide range of surgical applications and has been found to reduce postoperative pain, postoperative pain medication use, and the risk of CPSP.²

Incision sites should be infiltrated before and after surgery. Lidocaine traditionally is used for its rapid onset of action in reducing surgical site pain, but its short half-life may limit its applicability to postoperative pain. Recently, bupivacaine (half-life, 3.5 hours) and liposomal bupivacaine (24–34 hours) have gained more

attention. Both of these medications appear to be as effective as lidocaine in reducing surgical site pain.²⁴

Transversus abdominis plane (TAP) blocks have been used as an adjunct in pain management during abdominopelvic surgery. Although initial data on postoperative pain and opioid use reductions with TAP blocks were inconclusive,²⁵ more recent data showed a role for TAP blocks in a multimodal approach for reducing opioid use during laparoscopic and open surgery.^{26,27} Given the small number of studies on using liposomal bupivacaine for peripheral nerve blocks (eg, TAP blocks) in postoperative pain management, current data are inconclusive.²⁸

Postoperative management

The ERP approach calls for continuing multimodal analgesia after surgery—in most cases, scheduling early use of oral acetaminophen and ibuprofen, and providing short-acting, low-dose opioid analgesia as needed. All patients should be given a bowel regimen. Similar to undergoing prehabilitation for surgery, patients should prepare themselves for recovery. They should be encouraged to engage in early ambulation and oral intake and, when clinically appropriate, be given same-day discharge for minimally invasive surgical procedures.

Patients with chronic pain before surgery are at increased risk for suboptimal postoperative pain management, and those who are dependent on opioids require additional perioperative measures for adequate postoperative pain control. In these complicated cases, it is appropriate to enlist a pain specialist, potentially before surgery, to help plan perioperative and postoperative pain management.² Postoperative pain management for opioid-dependent patients should include pharmacologic and nonpharmacologic interventions, such as use of nonopioid medications (eg, gabapentin) and continuation of CBT. Patients with chronic pain should be closely followed up for assessment of postoperative pain control and recovery.

CASE Resolved

Surgical management is one aspect of the longer term multimodal pain management strategy for this patient. After preoperative pelvic floor physical therapy, she is receptive to starting a trial of an SNRI for her pain and mood symptoms. Both interventions allow for optimization of her preoperative physical and psychological status. Expectations are set that she will be discharged the day of surgery and that the surgery is but one component of her multimodal treatment plan.

In addition, before surgery, she takes oral acetaminophen, gabapentin, and celecoxib—previously having had no contraindications to these medications. During surgery, bupivacaine is used for infiltration of all incision sites, and the anesthesia team administers ketamine and a TAP block. After surgery, the patient is prepared for same-day discharge and given the NSAIDs and acetaminophen she is scheduled to take over the next

72 hours. She is also given a limited prescription for oxycodone for breakthrough pain. An office visit 1 to 2 weeks after surgery is scheduled.

ERP strategies for surgical management of endometriosis have not only improved this patient's postoperative recovery but also reduced her surgical stress response and subsequent transition to chronic postoperative pain. Many of the strategies used in this case are applicable to patients without chronic pain. ■

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3 cases of chronic pelvic pain managed with nonsurgical, nonopioid therapies

Chronic pain—different from acute injury or postsurgical pain—often arises from multiple organ systems. Three patient scenarios illustrate the importance of characterizing chronic pelvic pain and individualizing treatment to manage symptoms and improve quality of life.

Sara R. Till, MD, MPH, and Sawsan As-Sanie, MD, MPH

Chronic pelvic pain (CPP) is defined as noncyclic pain in the pelvis, anterior abdominal wall, back, or buttocks that has been present for at least 6 months and is severe enough to cause functional disability or require medical care.¹ CPP is very common, with an estimated prevalence of 15% to 20%. It accounts for 20% of gynecology visits and 15% of hysterectomies in the United States, and it is believed to account for \$2.8 billion in direct health care spending annually.²⁻⁵

Caring for patients with CPP can be very challenging. They often arrive at your office frustrated, having seen multiple providers or having undergone multiple surgeries. They may come to you whether you are a general ObGyn or subspecialize in maternal-fetal medicine, oncology, reproductive endocrinology, urogynecology, or adolescent gynecology. From interactions with other providers or their own family members, these patients may have received the message—either subtly or overtly—that their pain is “all in their head.” As such, some patients may resist any implication that their pain does not have an anatomic source. It is therefore critical to have appropriate tools for evaluating and managing the complex problem of CPP.

Perform a thorough and thoughtful assessment

Chronic pelvic pain often presents as a constellation of symptoms with contributions from multiple sources, as opposed to a single

disease entity. Occasionally there is a single cause of pain, such as a large endometrioma or degenerating fibroid, where surgery can be curative. But more commonly the pain arises from multiple organ systems. In such cases, surgery may be unnecessary and, often, can worsen pain.

Thoughtful evaluation is critical in the CPP population. Take a thorough patient history to determine the characteristics of pain (cyclic or constant, widespread or localized), exacerbating factors, sleep disturbances, fatigue, and current coping strategies. Focus a comprehensive physical examination on identifying the maneuvers that reproduce the patient’s pain, and include an examination of the pelvic floor muscles.⁶ In most cases, pelvic ultrasonography provides adequate evaluation for anatomic sources of pain.

Chronic pain does not behave like acute injury or postsurgical pain. Continuous peripheral pain signals for a prolonged period can lead to changes in how the brain processes pain; specifically, the brain can begin to amplify pain signals. This “central pain amplification” is characterized clinically by widespread pain, fatigue, sleep disturbances, memory difficulties, and somatic symptoms. Central pain amplification occurs in many chronic pain conditions, including fibromyalgia, interstitial cystitis, irritable bowel syndrome, low back pain, chronic headaches, and temporomandibular joint disorder.^{7,8} Recent clinical and functional magnetic resonance imaging (MRI) studies demonstrate central pain amplification in many patients with CPP.⁹⁻¹² Notably, these findings are independent of the presence or severity of endometriosis.

In this article we discuss many therapies that have not been specifically studied in patients with CPP, and treatment efficacy is extrapolated from other conditions with chronic pain amplification, such as fibromyalgia or interstitial cystitis. Additionally, many treatments for conditions associated with central pain amplification are used off-label, that is, the US Food and Drug Administration (FDA) has not approved the medication for treatment of these specific conditions. This should be disclosed to patients during counseling.

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Discuss treatment expectations with patients

Educating patients regarding the pathophysiology of chronic pain and setting reasonable expectations is the cornerstone of providing patient-centered care for this complex condition. We start most of our discussions about treatment options by telling patients that while we may not cure their pain, we will provide them with medical, surgical, and behavioral strategies that will reduce their pain, improve their function, and enhance their quality of life.

Surprisingly, most patients say that a cure is not their goal. They just want to feel better so they can return to work or activities, fully participate in family life, or not feel exhausted all the time. As such, a multimodal treatment plan is generally the best strategy for achieving a satisfactory improvement in symptoms.

CASE 1 Patient's pain continues after endometriosis excision

A 32-year-old woman (G1P1) reports having CPP for 8 years. She underwent excision of stage 1 endometriosis last year, which resulted in a modest improvement in pain for 6 months. Her pain is worse during menses, at the end of the day, and with vaginal intercourse (both during and lasting for 1 to 2 days after). On examination, you find diffuse pelvic floor tenderness but no adnexal masses or rectovaginal nodularity on palpation.

What treatment options would you consider for this patient?

Multimodal treatment often needed to manage CPP symptoms

The patient described in Case 1 may benefit from a combination of therapies that include analgesics, hormone suppression agents, and physical therapy (PT) (TABLE).

Analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen and naproxen, work by inhibiting cyclooxygenase enzyme, which decreases assembly of peripheral prostaglandins and thromboxane. In a large Cochrane review, NSAIDs were associated with moderate or excellent pain relief for approximately 50% of patients with dysmenorrhea, and they have been shown to reduce menstrual flow due to decreased production of

TABLE Treatments used in the management of chronic pelvic pain

Treatment	Type of pain
Analgesics	Dysmenorrhea, cyclic pain exacerbation
NSAIDs	
Acetaminophen	
Hormonal suppression	Menstrual exacerbation of pain symptoms, endometriosis
Combined estrogen-progestin agents	
Progestin-only agents	
GnRH agonists	
Pelvic floor physical therapy	Myofascial pain (reproduced by palpation of pelvic floor, abdominal wall, or paraspinal-lumbar muscles)
Antidepressants	Widespread pain, fatigue, sleep disturbances
TCA	
SNRIs	
Cyclobenzaprine	Myofascial pain, sleep disturbances, widespread pain
Calcium channel blockers	Widespread pain, fatigue, sleep disturbances
Gabapentin	
Pregabalin	
Anesthetic injections	Focal pain in a muscle or in distribution of an abdominal wall nerve
Lidocaine	
Bupivacaine	

Abbreviations: GnRH, gonadotropin-releasing hormone; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

uterine prostaglandins.¹³ There is little evidence for use of NSAIDs in chronic pain conditions.

Acetaminophen's mechanism of action is unclear, but the drug likely inhibits central prostaglandin synthesis, and it works synergistically with other analgesics.

Opioids act on μ and δ opioid receptors in the central and peripheral nervous systems as well as in the gastrointestinal system. No evidence supports opioid use in CPP or other chronic pain conditions. Long-term opioid use is associated with a multitude of adverse effects, risk for dependence, and the induction of opioid-induced hyperalgesia (in which patients develop greater sensitivity to pain stimuli).

Analgesics, specifically NSAIDs, can be considered for use in patients with dysmenorrhea, cyclic pain exacerbation, or a suspected inflammatory component of pain. Best practices include scheduling NSAID use before the onset of menses and continuing the drugs on a scheduled basis throughout. NSAIDs should be used for a brief period, and regular use on an empty stomach should be avoided.

Hormone suppression

Many types of hormone suppression therapy are available, including combined estrogen-progestin medications, progestin-only

medications, and gonadotropin-releasing hormone (GnRH) agonists and antagonists.

Combined estrogen-progestin medications include oral contraceptive pills (OCPs), vaginal rings, and transdermal patches. Combined estrogen-progestin methods cause atrophy of eutopic and ectopic endometrium and suppress GnRH.

Progestin-only methods include oral formulations, the levonorgestrel intrauterine device, intramuscular and subcuticular injections, and subdermal implants. Progestin-only methods lead to atrophy of eutopic and ectopic endometrium.

A GnRH agonist, leuprolide depot works by downregulating luteinizing hormone and follicle stimulating hormone release from the pituitary, causing suppression of ovarian follicular development and ovulation, leading to a hypoestrogenic state.

Combined estrogen-progestin formulations and progestin-only options are often considered first-line therapy for dysmenorrhea and endometriosis.¹³ Continuous administration, with the goal of inducing amenorrhea, is effective in the treatment of dysmenorrhea. Several randomized controlled trials have shown that different types of hormone suppression agents are, essentially, equally effective.^{13–15} Treatment recommendations therefore should focus on adverse effects, cost, and patient preference. GnRH agonists and norethindrone are not FDA approved for the treatment of endometriosis.

It may be appropriate to consider use of hormone suppression therapy in patients with menstrual exacerbation of pain symptoms, including those with a history of endometriosis. We generally advise patients that the goal is amenorrhea and that achieving it often involves a process of trying different formulations to find the best fit. Remember that GnRH agonists are dependent on a functional hypothalamic-pituitary-ovarian axis, and they are unlikely to be effective in women with suspected residual endometriosis who have had a bilateral oophorectomy.

Physical therapy

For CPP, PT typically targets musculoskeletal dysfunction in the pelvic floor, abdominal wall, hips, and back. Interventions include muscle control, mobilization, and biofeedback. Pelvic PT has been shown to improve pain and dyspareunia in patients with CPP, coccydynia, and vestibulodynia.^{16–18} One large study found a significant, patient-directed decrease in pain medication use after pelvic floor PT.¹⁹ Pelvic PT for patients with interstitial cystitis and pelvic floor tenderness resulted in improved pain and bladder symptoms.²⁰

Pelvic PT can be considered for patients with pain reproducible with palpation of the pelvic floor, abdominal wall, paraspinal-lumbar muscles, or sacroiliac joints. Best practices include referral to a therapist who has specialized training in CPP, including pelvic floor therapy. It is important to clearly list the indication for referral, as many of these therapists also treat stress urinary incontinence. The wrong exercises can result in increased hypercontractility of pelvic floor muscles, which can worsen pelvic pain.

It is also critical to clarify expectations with your patient at the time of PT referral. Specifically, advise patients that when beginning therapy, it is common to experience a temporary increase in discomfort of the pelvic muscles. Inform patients also to expect that their therapist will perform internal manipulation of the pelvic floor muscles through the vagina, as this can be surprising for some patients. Finally, counsel patients that their adherence to daily home exercises improves their chance of a durable, long-term successful response.²¹

CASE 1 Treatment recommendations

For treatment of this patient's CPP, consider scheduled naproxen therapy during menses, continuous OCPs, and referral for pelvic floor PT.

CASE 2 Patient with long-standing CPP, multiple diagnoses, and sleep problems

A 30-year-old woman (G2P2) reports having had CPP for 17 years. She is amenorrheic with continuous OCP treatment. She had experienced some improvement with pelvic PT. The patient reports that she has daily pain with intermittent pain flares and that she is exhausted and has poor sleep quality, which she attributes to pain. She has been diagnosed with interstitial cystitis, irritable bowel syndrome, and temporomandibular joint disorder. She has a history of depression, which she feels is well controlled with bupropion. Physical examination reveals that the patient has diffuse but mild pain in the pelvic floor and abdominal wall muscles.

What further pain management options can you offer for this patient?

Managing pain, sleep disturbance, and depression

This patient has been living with CPP for many years, and she has sleep difficulties that might be exacerbating pain or result from pain (or both). She is already on continuous OCPs and has had some relief with pelvic PT. Other options that may help with her multiple issues include antidepressants, cyclobenzaprine, and calcium channel blockers.

Antidepressants

Several classes of antidepressants have been used in the treatment of chronic pain conditions, specifically, tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Commonly used TCAs include amitriptyline, nortriptyline, desipramine, and doxepin. Commonly used SNRIs are duloxetine and milnacipran. Both TCAs and SNRIs increase the availability of norepinephrine and serotonin, which are thought to act on the descending pain inhibitory systems to decrease pain sensitivity. Of note, most selective serotonin reuptake inhibitors (SSRIs) at typical doses do not exert a significant enough impact on norepinephrine to be useful for chronic pain.²²

Evidence is limited on the use of antidepressants for treating CPP. Amitriptyline is the most extensively studied antidepressant. Amitriptyline treatment resulted in modest pain improvement in patients with CPP and fibromyalgia.^{23,24} Bothersome anticholinergic effects, including fatigue, dry mouth, and constipation, often are reported with TCAs. Adverse effects tend to be less with nortriptyline or desipramine compared with amitriptyline, but possibly at the expense of efficacy.

While SNRIs have not yet been studied in CPP, several investigations have shown that they improve pain and quality of life in fibromyalgia patients.^{22,25}

Antidepressant therapy may be appropriate for patients with suspected central pain amplification, widespread pain, and sleep disturbances. Best practices include patient education and careful discussion of this option with your patient. We suggest that clinicians explain that antidepressant medications alter the function of neurotransmitters, which modulate pain signals. While neurotransmitters also are involved in mood modulation, this is not the therapeutic goal in this circumstance. In addition, the doses used for the effective treatment of chronic pain are significantly lower than those needed to treat depression effectively.

Patients often need to hear that you believe that their pain is real and is not a manifestation of depression or another mood disorder. If you suspect that the patient also has untreated depression, address this as its own issue and use medications that have greater efficacy for mood symptoms.

Because many antidepressants can cause sedation, they are best taken before bedtime. Also, slow dose titration over several weeks will reduce the chance of bothersome adverse effects. Counsel patients that efficacy is not generally seen until at goal dose for several weeks. Be aware of interactions with other medications that can cause serotonin syndrome.

Cyclobenzaprine

Cyclobenzaprine is a muscle relaxant that also has activity in the central nervous system. The drug's precise mechanism of action is not known, but it appears to potentiate norepinephrine and bind to serotonin receptors. Thus, it also likely has some TCA-like activity.

Cyclobenzaprine has not been studied in patients with CPP. In fibromyalgia patients, however, it produced significant improvements in pain, sleep, fatigue, and tenderness.^{26,27} In our anecdotal experience with CPP patients, cyclobenzaprine has been one of the most impactful therapies. It hits the "chronic pain triad," meaning that it helps with myofascial pain, neuropathic pain, and sleep disturbances.

Cyclobenzaprine treatment may be considered for patients with myofascial pain, sleep disturbances, and clinical symptoms of central pain amplification. Best practices include starting with low (5 mg) scheduled doses at bedtime and slowly titrating the dose. Drowsiness is a very common side effect,

so we try to use that to the patient's advantage to help with sleep quality.

Notably, sleep disturbances are highly prevalent in patients with chronic pain.²⁸ The relationship appears to be bidirectional, meaning that chronic pain negatively impacts sleep quality, and poor sleep quality causes amplified perception of pain.²⁸⁻³⁰ Interventions that improve sleep quality have been associated with improvements in pain, coping, mood, and functional status.³¹ Helping a patient to improve her sleep generally requires a multifaceted approach. It always involves "sleep hygiene" or a behavioral component, and pharmacologic assistance may be considered when improved sleep hygiene does not provide adequately improved sleep quality.

Calcium channel blockers

Gabapentin and pregabalin are calcium channel blockers that inhibit the reuptake of glutamate, norepinephrine, and substance P, which helps to decrease pain sensitivity. They also act as membrane stabilizers, reducing hyperexcitability of peripheral and central nerves. Studies have shown that in patients with CPP, gabapentin resulted in improved pain and mood symptoms with few adverse effects.^{23,32} Patients with fibromyalgia had improvements in pain, sleep, quality of life, fatigue, and anxiety with both gabapentin and pregabalin.³³

It is appropriate to consider use of gabapentin or pregabalin in patients with central pain amplification and sleep disturbances. Best practices include starting with a low dose at bedtime. Traditionally, gabapentin is given in 3 equal doses throughout the day. In our experience, patients report less daytime drowsiness and better sleep quality if two-thirds of the daily dose is given at night, with the remaining daily dose broken up into 2 smaller daytime doses. Slow titration over several weeks will reduce risk of bothersome adverse effects. Patients should be counseled that efficacy is not generally seen until treatment is at goal dose for several weeks.

CASE 2 Treatment recommendations

For this patient with daily pelvic pain, multiple diagnoses that have a pain component, and poor sleep quality, consider a treatment plan that includes scheduled cyclobenzaprine, improved sleep hygiene, and, if needed, gabapentin.

CASE 3 Cesarean delivery, hysterectomy, and continued pelvic pain

A 38-year-old woman (G2P2) has had CPP for the past 10 years. She developed persistent left lower-quadrant pain after cesarean delivery of her son. She had a hysterectomy 2 years ago for CPP, after which her pain worsened. She describes daily pain with intermittent flares. On examination, the patient has focal left lower-quadrant pain lateral to the left apex of her Pfannenstiel incision.

What treatment approach would be appropriate for this patient?

Focal pain requires a precisely targeted treatment

This patient with focal left lower-quadrant pain is a candidate for anesthetic trigger point injections in the affected area near her Pfannenstiel incision.

Anesthetic injections

Consider the presence of trigger points and peripheral neuropathy in patients with focal abdominal wall pain. Trigger points are focal, palpable nodules within muscles. They are markedly painful to palpation and are associated with referred pain, motor dysfunction, and occasionally autonomic symptoms. They frequently are seen in abdominal wall or pelvic floor muscles in patients with CPP and are caused by abnormal neuromuscular depolarization.

The ilioinguinal, iliohypogastric, and genitofemoral nerves are in close proximity to Pfannenstiel and laparoscopic port site incisions. These nerves may be injured directly during surgery, but they also may be compressed by postoperative scarring.

Anesthetics, such as lidocaine and bupivacaine, which act as sodium channel blockers, can be injected into this area, and improvement often substantially outlasts the anesthetic's duration of action. While these drugs' mechanism of action is not clear, theories include altered function of sodium channels on sensory nerves with repeated anesthetic exposure, dry needling that occurs during injection, hydrodissection of tight connective tissue bands surrounding neuromuscular bundles, or depletion of substance P and neuropeptides as a result of injection.^{34,35}

In several studies, patients with CPP reported decreased pain with lidocaine injections in pelvic floor or abdominal wall trigger points.^{36–38} Patients with fibromyalgia reported improvement in pain and a decreased need for NSAIDs with bupivacaine trigger point injections.³⁹ While abdominal wall nerve blocks have not been extensively studied in patients with chronic neuropathic pain following gynecologic surgery, they have been shown to substantially improve chronic neuropathic pain following inguinal hernia repair.⁴⁰

Anesthetic injections appropriately may be considered in patients with focal pain in a muscle or in the distribution of abdominal wall nerves, palpation of which reproduces pain symptoms. Patients with diffuse pain are less likely to benefit from anesthetic injections. Best practices include careful examination with attention to areas of prior abdominal incisions.

Our practice is to inject each affected area with a mix of 9 mL of 1% lidocaine and 1 mL of sodium bicarbonate. If a patient reports at least 24 hours of improvement, we repeat the injection in 2 to 4 weeks. The goal is for the patient to experience a progressively longer duration of benefit with subsequent injections. We perform repeat injections shortly after pain begins to recur at that site. The patient should eventually graduate from receiving regular injections and may return for a remedial injection if pain recurs.

CASE 3 Treatment recommendations

For this patient with persistent focal left-lower quadrant pain and a defined trigger point near her Pfannenstiel incision, consider anesthetic injection in the left lower quadrant.

Work toward realistic symptom improvement

Remember that living with chronic pain is exhausting, and empathy with a patient-centered approach is the most important ingredient for patient improvement and satisfaction. Discuss realistic expectations with patients. Remind them that there is no magic bullet for the complex problem of CPP, and that chronic conditions generally do not improve overnight. Focus on improving the patient's function and quality of life, and applaud symptom improvement rather than focusing on complete pain resolution.

As these visits often require a good deal of patient education, budget more appointment time if feasible. We find that scheduling frequent return visits (approximately every 3 to 4 months) allows timely treatment follow-up so that changes may be made if needed. If you have maximized your available treatment options, referring the patient to a specialist with additional training in CPP is a sensible next step. ■

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