CHAPTER 35

Chronic Pain after Surgery

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Approximately 40 million surgical procedures take place across North America each year, and by most conservative estimates 10% to 15% of those patients will go on to suffer chronic pain 1 year after surgery.[1] This is a silent epidemic of devastating proportions for those who suffer the pain and the associated emotional costs related to distress and for society as a whole who bear the financial cost of lost productivity and treatment of pain-related problems. Investigations in recent years have given better definitions of the extent of the problem, some of the factors that may predict the onset of chronic pain after surgery and methods of preventing chronic pain. In addition the future will bring us better definitions of the genetic basis of development of chronic pain allowing us to better counsel patients prior to different types of surgery regarding risk of chronic pain in relation to surgery and possibly allowing us to better aim the most intensive treatments at those patients in order to reduce morbidity. This chapter will discuss the extent of the problem of chronic postsurgical pain (CPSP), the factors associated with development, the typical presentation of CPSP, the genetics of CPSP, and possible methods of preventing CPSP.

WHAT IS CHRONIC PAIN AFTER SURGERY?

Without a good definition it is not possible to estimate the extent of a problem. Very few papers examining the epidemiology of chronic pain after surgery have used a consistent definition. This absence has led to large variability in estimation of chronic pain across different studies and has slowed progress in acquisition of knowledge in this area.

In their original paper on chronic pain after surgery, Crombie et al.[1] proposed a working definition as follows:

1. The pain should have developed after a surgical procedure.
2. The pain should be of at least 2 months duration.
3. Other causes of the pain should be excluded, such as recurrence of malignancy or infection.
4. The possibility that the pain is continuing from a preexisting problem should be explored and exclusion attempted.

This was the first worthy attempt to define CPSP and future studies would benefit from using such a consistent definition. However, an obvious problem with this definition is that some types of CPSP are related to a preexisting preoperative painful condition, such as phantom limb pain. Nevertheless, the use of a consistent definition of CPSP in the future will significantly help accurate description of the extent of the problem and allow better focus on the areas of greatest need.

EPIDEMIOLOGY OF CHRONIC PAIN AFTER SURGERY

The incidence of CPSP varies significantly by site of surgical procedure (Table 35-1); however, most reports support an incidence of at least 10% of patients having pain 1 year after surgery. Several high-quality reviews since the 1990s have highlighted the problem of chronic pain after surgery. Crombie et al.[1] highlighted the problem with their survey of greater than 5000 patients presenting to North British pain clinics, and found that surgery contributed to pain in 22.5% of those patients. In particular, pain in the abdomen, anal, perineal, and genital pain was associated with surgical procedures. Perkins and Kehlet[2] reviewed the evidence for CPSP and found an incidence of phantom limb pain of 30% to 81%, greater than 50% for chronic post-thoracotomy pain, postmastectomy pain syndrome in 11% to 57%, phantom breast pain in 13% to 24%, and post–breast surgery arm and shoulder pain in 12% to 51%. Chronic pain after cholecystectomy is common (3% to 56%) and the overall incidence of chronic pain after inguinal hernia surgery is 11.5%.

Despite improvements in methods of providing acute pain control since the 1990s, there have been no dramatic improvements in the incidence of CPSP. Studies examining pain after inguinal hernia repair,[3] breast surgery,[4] thoracic surgery,[5] and hip surgery[6] indicate that a very conservative estimate of approximately 10% of patients continue to suffer chronic pain following many types of surgery.

FACTORS ASSOCIATED WITH CHRONIC PAIN AFTER SURGERY

Factors that are associated with an increased likelihood of developing CPSP are summarized in Table 35-2. It is not known at the present time whether all of these factors are causally related (as opposed to associations) to development of chronic pain. These factors can be divided into preoperative, intraoperative, and postoperative factors. Preoperative factors include moderate to severe preoperative chronic pain, repeat surgery, and psychological factors. Intraoperative factors include surgery in a low-volume center, surgical approach (open vs. laparoscopic), and intraoperative nerve injury. Postoperative factors include acute pain (moderate to severe), radiation therapy, and neurotoxic chemotherapy.

Preoperative Factors

A consistent factor associated with development of acute and CPSP across many types of surgery is the presence of preoperative pain. This is of particular relevance to

TABLE 35–1 Incidence of Chronic Pain after Surgery by Surgical Site

Study	Surgical Procedure	Patients with Data	Follow-up	Incidence of Chronic Pain
Nikolajsen et al. 1997	Amputation	60	1 yr	Phantom pain 70%
Richardson et al. 2006	Amputation	52	6 mo	Phantom pain 78.8%
Jensen et al. 1985	Amputation	58	2 yrs	Phantom pain 59%
Tasmuth et al. 1997	Breast surgery	93	1 yr	13–33%
Nikolajsen et al. 1997	Cesarean section	220	1 yr	Scar pain 12.3%
Aasvang	Hernia repair	694	1 yr	56.6%
Grant et al. 2004	Hernia repair	750	5 yr	19% groin pain
Nikolajsen et al. 2006	Hip replacement	1048	12–18 mo prevalence	12.1% moderate–very severe pain
Borly et al. 1999	Open cholecystectomy	80	1 yr	26%
Meyerson et al. 2001	Sternotomy for cardiac surgery	318	1 yr	28%
Katz et al. 1996	Thoracotomy	23	18 mo	52%
Pertunnen et al. 1999	Thoracotomy	67	1 yr	61%
Gotoda et al. 2001	Thoracotomy	91	1 yr	41%

TABLE 35–2 Factors Associated with Development of Chronic Pain after Surgery

Preoperative Factors	Intraoperative Factors	Postoperative Factors
Moderate–severe pain of >1 mo duration	Surgical approach with risk of nerve injury	Moderate–severe acute pain
Repeat surgery	Nonlaparoscopic technique	Neurotoxic chemotherapy
Psychological factors	Surgery in low-volume center	Radiation therapy to site

anesthesiologists because we are often the main advocate for good quality postoperative pain management. The presence of preoperative pain is a risk factor for the development of early acute postoperative pain, pain in the days, weeks, and months following surgery.[7] A further amplifying factor is that the presence of severe acute postoperative pain also is a risk factor for development of chronic postsurgical pain. Kalkman et al.[8] examined preoperative factors predicting severe acute pain after surgery and found independent predictors of severe pain including preoperative pain, female gender, younger age, incision size, and type of surgery. Thomas et al.[9] examined patients having hip or knee replacement and spinal decompressive surgery and also found that predictors of severe postoperative pain included preoperative pain, female gender, and younger age. A very consistent factor in the development of CPSP is the presence of either severe preoperative pain, postoperative pain, or both. No other patient factor is as consistently related to the development of CPSP as pain itself.

Several factors may explain the consistent relationship of preoperative and severe acute postoperative pain predicting CPSP,[7] including the following:

1. Preoperative opioid tolerance leading to underestimation and underdosing of postoperative opioid analgesics.
2. Intraoperative nerve damage and the associated central nervous system changes such a central sensitization and "wind-up."
3. Sensitization of pain nociceptors in the surgical field.
4. Postoperative ectopic activity in injured primary afferents and collateral sprouting from intact nociceptive Aδ-afferents neighboring the area supplied by injured afferents.
5. Central sensitization induced by the surgery and maintained by further input from the surgical site during the healing process.
6. Structural changes in the central nervous system (plasticity) induced by nociceptive inputs with consequent reduction in normal inhibitory control systems leading to "centralization" of pain and development of pain memories.
7. Heretofore unidentified pain genes that may confer increased risk of developing both severe acute and chronic postsurgical pain.
8. Psychological and emotional factors such as emotional numbing and catastrophizing (see next page).
9. Social and environmental factors such as solicitous responding from significant others and social support (see next page).
10. Response bias over time—that is, some individuals have a tendency to report more pain than other individuals.
11. Publication bias in which findings of a significant relationship between pain before and after surgery are published, whereas negative findings are rejected and do not get published.

Psychosocial Factors

Several psychosocial predictors of chronic postsurgical pain have been identified including increased preoperative anxiety,[11] an introverted personality, less catastrophizing, social support and solicitous responding in the week after amputation, higher emotional numbing scores at 6 and 12 months,[12] fear of surgery, and "psychic vulnerability."[13]

Pain catastrophizing relates to unrealistic beliefs that the current situation will lead to the worst possible pain outcome. Consistently in the pain literature chronic pain patients who do not catastrophize fare better than patients who do. It is therefore somewhat paradoxical that the opposite has been found in the prediction of patients who are at risk of CPSP and may be an artifact of the method by which data were collected.[11]

Solicitous responding refers to the behaviors on the part of spouses or significant others who unwittingly reinforce patients' negative behaviors and thereby increase their frequency of occurrence. For example, an empathic spouse may reinforce negative behavior by insisting that her partner rest when in fact a more appropriate response would be to encourage activity. Such solicitous behaviors may in fact have the unintended consequence of increasing pain-related behaviors and contributing to pain-related disability. The reader is directed to the comprehensive review by Katz and Seltzer for further information.[7]

Intraoperative Factors

Three main surgical factors have a possible influence on the incidence of CPSP:

Experience of the surgeon. The experience of the surgeon can affect morbidity following surgery. Tasmuth et al.[14] studied patients after breast cancer surgery and found that patients who had surgery in low-volume units suffered more CPSP than patients in specialist units where higher numbers of patients had surgery. Other studies, however, have shown equivocal results. Courtney et al.[15] demonstrated no correlation between the grade of surgeon and severe pain after hernia repair.

Avoidance of intraoperative nerve injury. Many basic science studies have successfully demonstrated that intentional nerve injury in animals produces behaviors that resemble symptoms of neuropathic pain in humans. It would therefore make sense during surgical procedures on humans to reduce, as much as possible, any chance of causing intraoperative nerve injury. Many CPSP syndromes occur following surgery around significant nerve structures. Examples include pain after inguinal hernia repair (ilioinguinal and iliohypogastric nerves), axillary dissection (intercostobrachial nerve), and post-thoracotomy pain (intercostal nerves). When a nerve is injured, it emits a long-lasting, high-frequency burst of activity.[16–17] This activity is transmitted to the central nervous system where the massive excitatory stimulus activates postsynaptic NMDA receptors, leading to excitotoxic destruction of inhibitory interneurons,[18] disinhibition of pain pathways, and increased postoperative pain. The avoidance of intraoperative nerve injury would be a useful preventive measure and should be attempted wherever possible.

Use of minimally invasive surgical techniques where possible. Although the size of the surgical procedure does not correlate well with the incidence of CPSP, the type of procedure and how it is performed can influence CPSP. Wallace and colleagues studied incidence of chronic pain after different types of breast surgery and found that mastectomy had a much greater incidence of CPSP (53%) compared to breast reduction surgery (22%).[19] Cholecystectomy appears to show significant reductions in CPSP when a laparoscopic technique is used as compared to an open approach and these results have been confirmed by several studies.[20,21]

Genetic Factors

The study of the genetics of pain is in its infancy and there are no current research reports that provide data on genes that may predispose patients to CPSP. There are only a handful of reports that identify polymorphisms in human genes associated with chronic pain, including COMT (encoding catechol-O-methyl transferase), and 5-HTTLPR (the gene encoding the serotonin transporter), which has been found to associate significantly with severity of migraine,[22] burning mouth syndrome,[23] irritable bowel syndrome, and fibromyalgia. IL1RN (encoding the IL-1 receptor antagonist) and MC1R (encoding the melanocortin-1 receptor) in vulvodynia, IL23R in Crohn's disease, and GCH1 (encoding GTP cyclohydrolase, an enzyme catalyzing tetrahydrobiopterin, BH4, an essential co-factor for catecholamine, serotonin and nitric oxide production) have been implicated in persistent radicular pain following discectomy. Recent work has examined OPRM1 (encoding the μ-opioid receptor), including a systematic review[24] that attempted to determine the relationship of this gene to opioid sensitivity, side effects, or pain levels. Only 7% of the overall variance could be explained by genetic factors, and the authors concluded that only a minor degree of variance in the clinical setting could be related to pharmacogenetic factors. Despite the evidence of association between other genes and chronic pain conditions at this time any plan to incorporate genotyping information into the ability to predict who will develop chronic pain is premature.[25] Genetic factors relating to CPSP bear much promise; however, it is clear that significant amounts of work need to be done before they become useful in clinical practice.

PREVENTION OF CHRONIC PAIN AFTER SURGERY

Of the factors that are associated with generation of CPSP, several are within the direct control of anesthesiologists and surgeons in the perioperative period. Several studies have now demonstrated that severe acute pain after surgery is associated with an increased incidence of chronic pain. In a landmark study, Katz et al.[26] examined patients who had undergone lateral thoracotomy 18 months earlier and found that 52% of patients reported chronic pain. Of many factors, early severe postoperative pain was the only factor that significantly predicted development of long-term pain. In a study of trauma patients undergoing elective surgery, greater acute pain on postoperative day 4 was associated with

CPSP.[27] Iohom et al. recently examined the effect of a multimodal regimen on patients having breast cancer surgery and demonstrated a relationship between severe postoperative pain and subsequent CPSP.[28]

The relationship between severe acute pain and subsequent chronic pain is all the more worrying given that it appears a high proportion of patients continue to suffer moderate to extreme levels of pain after surgery.[29] Attempts to adequately prevent or treat severe acute pain may reduce the incidence of chronic pain. In addition, the ability to avoid intraoperative nerve injury and minimally invasive operative techniques both appear to reduce the chances of developing CPSP.

PREVENTIVE ANALGESIA

If severe acute pain after surgery can predispose to CPSP it follows that prevention of acute pain after surgery may help to reduce the incidence. In anesthesia and acute pain management, the practice of treating pain only after it occurs is slowly being replaced by a preventive approach. Although these methods have been developed primarily for reducing acute pain, the secondary aim of reducing transition to chronicity has also been a significant motivation. The theory that acute postoperative pain might be intensified by central sensitization induced by surgery was originally conceived by Crile[30] and later advocated by Wall[31] who suggested that "preemptive preoperative analgesia" would block central sensitization caused by surgical insult and thus reduce the severity of acute postoperative pain. Subsequent attempts to validate this concept of "preemptive analgesia" were limited by an overzealous definition attempting to prove that a preincisional intervention would be superior to the same intervention following incision.[32] This definition was flawed because surgical insult causing sensitization would be expected to occur throughout surgery and for several hours or days afterward. It was therefore really no great surprise that a subsequent meta-analysis[33] demonstrated no benefit of preemptive analgesia according to this definition. More recently, a more clinically relevant term—*preventive analgesia*—has been developed.[34] Preventive analgesia refers to the attempt block nociceptive input through the application of several analgesic agents acting at different sites (multimodal analgesia) starting prior to surgery and continuing for several hours or days following surgery. A successful preventive analgesic intervention would reduce or ablate pain for hours, days, or weeks following surgery and well beyond the duration of action of the initial analgesic intervention.[35] Several studies that have examined best analgesic methods including preventive analgesia have demonstrated benefits and these are described in the following sections according to the type of intervention.

LOCAL ANESTHETIC TECHNIQUES

Epidural analgesia provides significant acute pain benefits in the early perioperative period, especially for major abdominal and thoracic surgery, and several large studies have demonstrated these benefits.[36] However, the ability to prevent progression to chronicity has been less effective, with mixed results across several studies. Lavand'homme et al.[37] compared the epidural or intravenous route using local anesthetic, an opioid, or clonidine in one of four groups for patients undergoing major abdominal surgery. All patients received a bolus and infusion of low dose ketamine started preincision and maintained throughout the procedure. Patients in the intravenous alone group had much higher pain scores at rest and with movement compared to the other groups. The incidence of chronic pain in the intravenous alone group was significantly greater at 6 months (48%) and 12 months (28%) than other groups who had been given an epidural technique.

Gottschalk et al.[38] examined men undergoing radical prostatectomy randomizing either to epidural bupivacaine, fentanyl, or saline, followed by postoperative, patient-controlled epidural analgesia. Acute pain in the hospital was greatly reduced for the two groups who had been treated prior to incision, and incidence of pain 9.5 weeks (though not at 3.5 or 5.5 weeks) following surgery was significantly lower in the groups who had been treated in this way.

For patients having thoracotomy, Obata et al.[39] compared patients receiving preincisional epidural mepivacaine compared to the same intervention at the completion of surgery. Assessments at 3 and 6 months after surgery showed a significant reduction in post-thoracotomy pain in patients who received the preincisional epidural mepivacaine. Sentürk et al.[40] demonstrated significant benefit of an epidural compared to intravenous analgesic technique when used for patients having thoracotomy with patients in the epidural groups having significantly lower incidence and intensity of chronic post-thoracotomy pain. However, Ochroch et al.,[41] when randomizing patients to epidural bupivacaine and fentanyl either preincision or after rib approximation, could not demonstrate any differences in chronic pain 48 weeks after surgery.

The use of epidural analgesia for prevention of chronic phantom limb pain has been less effective. Despite early promise of the benefits of epidural analgesia in preventing postamputation pain a more rigorous study by Nikolajsen et al.[42] failed to demonstrate benefit. Up until recently, peripheral nerve blocks alone have had a disappointing effect on the incidence of CPSP despite their clear benefits in reducing acute postoperative pain. McCartney et al.[43] randomized 100 patients to either axillary block or general anesthesia for ambulatory upper limb surgery and despite significantly improved perioperative outcomes patients had identical incidence of pain 2 weeks following surgery. However, Iohom et al.[28] compared a multimodal analgesic regimen including both a paravertebral catheter and an intravenous COX2 inhibitor (parecoxib) followed by oral celecoxib with a standard treatment group (including postoperative diclofenac) for patients having breast cancer surgery. Patients in the paravertebral catheter group had significantly less acute pain and also a lower incidence of chronic pain at 2 to 3 months following surgery (0% vs. 85%).

NMDA RECEPTOR ANTAGONISTS

NMDA receptors play an important role in acute pain hypersensitivity states and the generation of CPSP. Several studies have demonstrated benefits of NMDA receptor antagonists in the prevention of pain following surgery.

McCartney et al. systematically reviewed this area,[35] and determined that both ketamine and dextromethorphan provide analgesic benefits beyond the clinical duration of action of either drug (5 half-lives). Longer-duration benefits are more controversial. Katz et al.[44] examined both short- and long-term effects of preoperative or postincisional intravenous fentanyl and low-dose intravenous ketamine, compared to a standard treatment receiving fentanyl but not ketamine, on postoperative pain on men undergoing radial prostatectomy under general anesthesia. Pain scores did not differ at any time during the first 3 postoperative days, although by the third day the hourly rate of opioid consumption was significantly less in the pretreated group. Unfortunately, no differences were seen in pain outcomes at 2 weeks and 6 months following surgery. Schley et al.[45] compared two groups of patients undergoing unilateral upper extremity amputation under continuous brachial plexus block. The treatment group also received a daily dose of the NMDA receptor antagonist memantine. In addition to improved acute pain control, the memantine group also had less chronic phantom pain at 4 weeks and 6 months (but not at 12 months) after surgery. Remérand et al.[46] studied patients having total hip arthroplasty under general anesthesia and randomized the treatment group to receive a preoperative bolus and then 24 hr continuous infusion of intravenous ketamine. At postoperative day 30, the ketamine group had less need for two crutches or a walking frame, and from day 30 to 180 decreased the number of patients with persistent pain at rest in the operated hip ($p=0.008$). However, Sen et al.[47] also compared ketamine, gabapentin, and placebo for patients having hysterectomy, and found that although opioid consumption was reduced in both ketamine and gabapentin groups only the gabapentin group had reduced incidence of incisional pain scores at the 1-, 3-, and 6-month follow-up visits.

GABAPENTIN AND PREGABALIN

Both gabapentin and pregabalin bind to the α2δ unit of the calcium channel and are useful components of multimodal analgesia, producing opioid sparing effects and reducing the severity of acute postoperative pain. A number of studies have also examined their effect on CPSP.[48] Fassoulaki et al.[49] randomized 50 patients having breast cancer surgery to either multimodal analgesia including gabapentin or placebo control. At 3 but not 6 months after surgery, patients in the multimodal group had significantly lower incidence of axilla pain (14 vs. 45%), morning pain (23% vs. 59%), and analgesic use (0% vs. 23%) compared with the placebo control patients.

Brogly et al.[50] examined the effect of gabapentin 1200 mg compared to placebo in a randomized study of 50 patients having thyroidectomy under general anesthesia. All patients also received a bilateral superficial cervical plexus block after induction. Although there were no obvious differences in acute pain (possibly masked by the cervical plexus block) patients in the gabapentin group did have a significantly lower incidence of neuropathic pain (4.3% vs. 29.2%) 6 months following surgery.

Buvanendran et al.[51] examined the effects of perioperative oral pregabalin started before total knee arthroplasty and continued for 14 days after surgery. Patients receiving oral pregabalin had less acute pain and also less neuropathic pain at 3 and 6 months following surgery. However, an earlier randomized study by Fassoulaki et al.[52] randomized patients having breast surgery to gabapentin, mexilitine, or placebo, and although they demonstrated better acute pain control, there was no difference in pain at 3 months following surgery.

NSAIDs

Nonsteroidal anti-inflammatory drugs have powerful analgesic effects and are effective components of a multimodal analgesic regimen for acute postoperative pain control. It is less certain at this time if they have any impact on the incidence of CPSP.

PREVENTIVE ANALGESIA SUMMARY

It is clear across numerous studies that providing effective acute pain control is best performed using multimodal analgesic techniques, including local anesthetics, opioids, and other agents such as NMDA receptor antagonists and/or gabapentin and associated drugs. Several studies indicate that there is an association between better acute pain control and reduction in CPSP. It would therefore seem wise to strive for best acute pain control for our patients in the knowledge that for some patients and procedures this will also translate into better long-term outcomes.

FUTURE STRATEGIES FOR PREVENTING CPSP

Good perioperative analgesia and minimization of surgical tissue injury will remain important goals for both anesthesiologist and surgeon in the perioperative period. The broader and more consistent use of multimodal analgesic techniques remain the simplest current method by which anesthesiologists could have a major impact on the development of CPSP. Screening strategies for psychological risk factors may be an important method in high-risk surgical procedures such as breast and thoracic surgery. Identification of the high-risk patient will allow more effective targeting of such patients with potent analgesic techniques in the perioperative period. The use of genetic screening for patients at risk of CPSP remains elusive and much more research will be required before this strategy becomes a reality.

Several interesting avenues of research focusing on novel analgesic targets are being developed, including GDNF[53] (glial-cell-line–derived neurotrophic factor), NK-1 (neurokinin 1) receptor antagonists,[54] voltage-gated Na channel blockade,[55] and purinergic receptor antagonists.[56]

CONCLUSION

Most people will experience surgery of one sort or another during their lifetime, and for a significant proportion this will lead to CPSP. The development of CPSP is common and dependent on numerous factors (Fig. 35-1). At the present time, anesthesiologists can make a difference by providing effective treatment of postoperative pain by including at least two modalities of multimodal analgesia, preferably starting before surgical incision. Other factors, including avoidance of intraoperative nerve injury and minimally

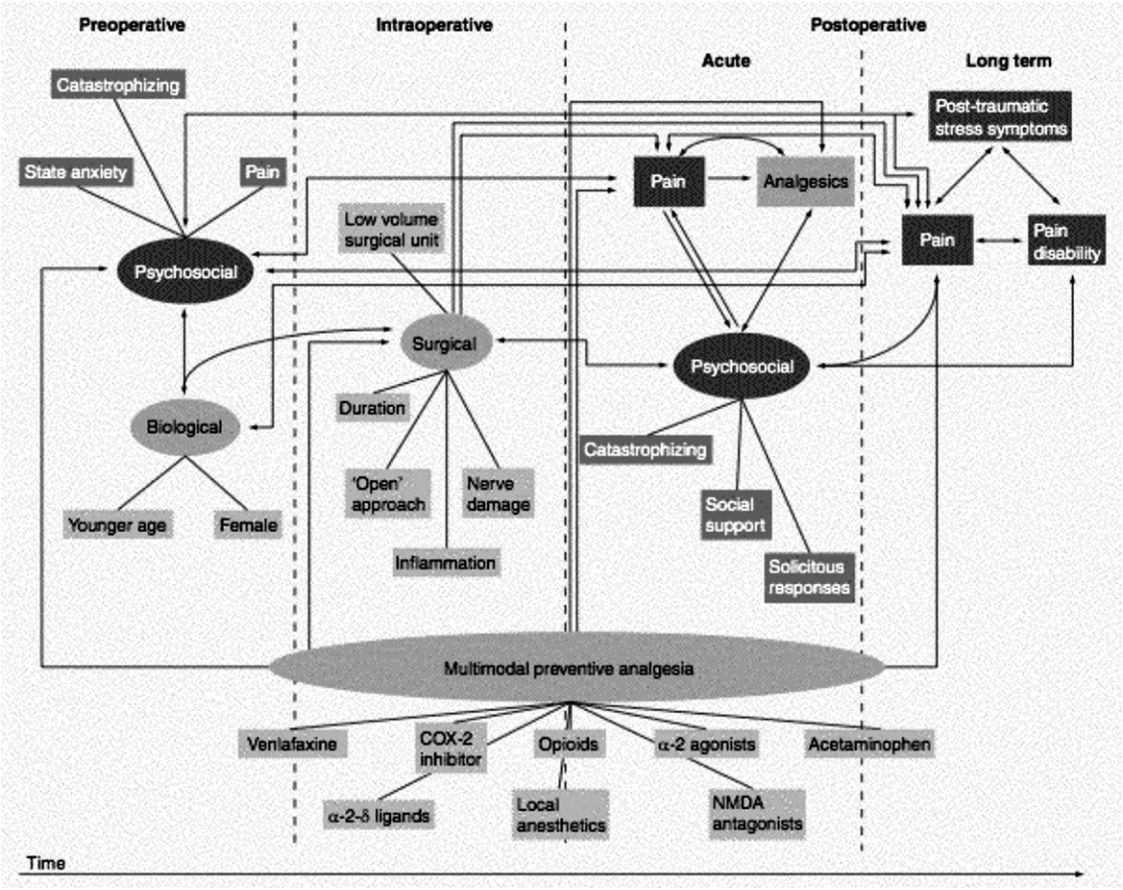

FIGURE 35-1 Schematic diagram of the processes involved in the development of chronic postsurgical pain showing the relationship between preoperative, intraoperative, and postoperative factors. *(From Katz J, Seltzer Z: Transition from acute to chronic postsurgical pain: risk factors and protective factors.* Expert Rev Neurother *9:723–744, 2009.)*

invasive techniques, may also help to reduce incidence of CPSP. Factors such as patient psychological and genetic factors are less easy to control; however, better understanding of these in the future may allow patients to properly consider the risks of developing CPSP and use aggressive and/or novel treatments to optimally prevent and manage CPSP.

KEY POINTS

- Chronic pain after surgery is common.
- Risk factors include patients with preexisting pain, psychosocial factors, age, gender, and possibly genetic susceptibility.
- CPSP can be prevented using good surgical technique (avoiding nerve damage and using minimally invasive techniques) and aggressive multimodal analgesia starting immediately prior to surgery.
- Future strategies should include more consistent use of multimodal analgesia across surgical populations and screening for high-risk patients using psychological and genetic factors.

REFERENCES

Access the reference list online at http://www.expertconsult.com