Chronic postsurgical pain (CPSP) has gained recognition as a significant adverse outcome following many different types of surgeries. The presence of some degree of postsurgical pain is expected following various procedures; however, many patients go on to develop continuous and persistent pain that is severe enough to hinder their quality of life years after their initial surgery. The complex transition
from acute to chronic pain has been an area of intense focus, and researchers are aiming to understand the mechanisms involved in changing a patient’s processing of pain after initial introduction of painful stimuli. Studies on this transition from acute to chronic pain have focused on the continuum of biochemical and pathophysiologic changes in the pain pathways of the peripheral and central nervous systems (CNS). Recent efforts have aimed to understand how perioperative pain management, surgical, genetic, psychosocial, and other patient factors contribute to the development of chronic pain. Improved understanding of the interrelated physiologic, psychologic, and perioperative factors that influence pain mechanisms is critical to the development of predictive models that will guide preventative interventions for those at risk and therapies for those already with CPSP.

**METHODS**

Medline and Cochrane databases were reviewed to identify publications relevant to CPSP pathophysiology, risk factors, predictive models, and prevention. Publications were selected based on author expertise to summarize our current understanding of the CPSP.

**RESULTS**

**Acute Pain Physiology and the Transition to Chronic Pain**

The physiology behind acute pain is a complex and well-studied process with many mechanisms in place to prevent aberrant sustained perception of transient noxious and perception of nonnoxious stimuli as pain. In the case of chronic pain, there have been changes in these homeostatic processes leading to perception of pain, even after removal of a noxious insult.

**Signal Transduction**

Pain perception, or nociception, originates from the site of mechanical or chemical noxious stimuli. Nociceptors sense such stimuli through free nerve endings of primary afferent Aδ and C sensory fibers, which respond to a variety of inflammatory mediators released from damaged cells and surrounding immune cells. These mediators include potassium, adenosine-3,5-triphosphate, sodium, protons, nerve growth factor (NGF), tumor necrosis factor-alpha (TNF-α), prostaglandins, Bradykinins, histamines, and interleukins (1,2). Amplification of this initial inflammatory event can occur with the release of substance P, calcitonin gene-related peptide (CGRP), neurokinin A, and nitric oxide (NO) (3).

**Transmission to CNS**

As these excitatory substances interact with receptors located on the free nerve endings of the primary afferent fibers, the nerve membranes are depolarized, generating action potentials that travel along the fibers to the spinal cord. These Aδ and C sensory nerve fibers have their cell bodies clustered at the dorsal root ganglion (DRG). Aδ fibers are lightly myelinated, fast-conducting nerves that are responsible for the initial response to noxious mechanical and thermal stimuli. They are associated with sharp, localized pain. C fibers are unmyelinated, slow-conducting nerves that have higher activation thresholds in their nonsensitized state than Aδ fibers. They respond to more intense noxious stimuli and are responsible for dull, diffuse pain (4). A third type of primary afferent nerve, Aβ fibers, are highly myelinated and have a very high conduction velocity. They are low-threshold and usually transmit nonnoxious stimuli such as light touch.

Aδ and C fibers synapse with secondary afferent neurons in Rexed laminae I and II within the dorsal horn of the spinal cord, whereas Aβ fibers generally synapse in laminae III-VI (5). The postsynaptic secondary afferent neurons respond to neurotransmitters including glutamate and substance P released by the primary afferent Aδ and C fibers. Glutamate targets alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors on the secondary afferent neurons, whereas substance P activates neurokinin 1 receptors on the secondary afferent neurons within lamina I (3,6). Both glutamate and substance P also influence the activation of microglial cells in the CNS (5,7). These secondary afferent neurons are wide dynamic range (WDR) neurons, and respond to input from nociceptive Aδ and C fibers in addition to usually innocuous Aβ fibers (6).

**Transmission to Thalamus**

Secondary afferent neurons ascend up the spinal cord from the dorsal horn in an area of white matter called the spinothalamic tract. The neurons that travel up this main pathway synapse with third-order neurons in the thalamus and transmit signals that are important for pain localization (8). Secondary afferent neurons also transmit nociceptive signals through the spinothalamic tract to the brainstem reticular formation before projecting to the thalamus, and through
the spinoparabrachial and spinomesencephalic tracts to the brainstem and medulla (4,8). The spinoreticular tract in particular is responsible for individualized pain responses relating to emotion (8).

Important mechanisms exist to inhibit these ascending nociceptive pathways in the CNS. Inhibitory pain modulation within the spinal cord occurs in a process described by Melzack and Wall’s gate control theory of pain. The transmission of nonnoxious stimuli by Aβ fibers activates interneurons within the spinal cord that act to inhibit nociceptive signals from C fibers (4). Gamma-amino butyric acid (GABA) and glycine interneurons in the dorsal horn are 2 such inhibitory neurons that mediate overall nociceptive transmission (5). The predominance of ascending pain pathways over these interneuronal inhibitory systems following inflammation or injury, in conjunction with changes in the brain regions that activate them, are significant contributors in the development of enhanced pain response states (4).

Transmission to Cerebral Cortex

Third-order neurons within the spinothalamic tract project up from the thalamus to the somatosensory cortex and many other areas involved in nociception collectively known as the brain’s pain matrix. Nociception within the brain first involves the nociceptive cortical matrix, which is responsible for the initial fast-acting pain response (9). The second-order perceptual matrix is then associated with individualized emotional responses to pain.

The perceptual matrix, the periaqueductal gray matter (PAG), rostral ventromedial medulla (RVM), and reticular formation are particularly important to the modulation of ascending nociceptive pathways. Descending inhibitory pathways originating in the PAG and RVM travel down to the dorsal horn and release noradrenaline and serotonin, which act in opposition to the neurotransmitters released from primary afferent neurons. This largely results from the abundance of endogenous opioids and opioid receptors in these brain areas, and the dysfunction or weakening of this endogenous inhibitory system, stemming from certain patient conditions, may lead to an increased likelihood of chronic pain development (4,6).

Primary Afferent Sensitization

Persistent nociceptive stimulation in the peripheral nervous system can lead to pathophysiological changes in nociceptive pathways due to neuroplasticity. When primary afferent fibers are activated and release inflammatory molecules such as interleukin-1B, interleukin-6, NGF, and TNF-α, they induce the release of histamine from nearby mast cells. Histamine further induces C fibers to release substance P and CGRP, resulting in a process known as neurogenic inflammation (10,11). Additionally, the inflammatory molecules increase the activation of receptors such as transient receptor potential 1, which become more responsive owing to the reduction of their activation thresholds (1,10).

Intracellular signal-transduction cascades also upregulate nociceptive sodium ion channels and influence the phosphorylation of transducers protein kinase A and protein kinase C (11,12). These series of changes result in a hyperexcitable neuronal state, which precipitates primary hyperalgesia in patients (3).

Secondary Afferent Sensitization

During the process of secondary sensitization, glutamate has an important excitatory effect on NMDA receptors located on postsynaptic neurons, which usually do not respond to nociceptive signals. Continuous glutamate release from C fibers causes an extended depolarization of secondary afferent neurons in the dorsal horn, facilitating the removal of the Mg2+ block from NMDA receptors. This allows glutamate to bind to the receptors so that any subsequent activation of WDR neurons by normally innocuous signals through Aβ fibers causes a pain response to nonnoxious stimuli, known as allodynia (1).

CNS glial cells respond to excitatory molecules released from primary afferent terminals, in addition to NO and prostaglandins released from secondary afferent neurons (7). Activated glial cells then upregulate cyclooxygenase-2 (COX-2) to produce prostaglandin E2, and release a variety of excitatory substances including interleukin-1, interleukin-6, and TNF-α (1,7). These substances lead to the further activation of COX-2, reduced activation thresholds in secondary afferent neurons, and upregulation of AMPA and NMDA receptors (1). Other significant alterations in secondary neuron connectivity include the increased concentration of noxious tetrodotoxin-resistant sodium channels, and the cell death of antinociceptive GABAergic and glycine-ergic interneurons (3,7). The resulting sensitization of the CNS plays an important role in the development of neuropathic pain and leads to increased sensitivity to noxious stimuli of the area surrounding injured tissue, known as secondary hyperalgesia (1).

Understanding of the pathophysiological aberrancies underlying CPSP will continue to be foundational.
in guiding research and management moving forward. Targeting of the physiologic and anatomic pathways involved will aid in implementing clinically supported preventative and therapeutic measure to address CPSP.

**Predisposing Risk Factors**

A variety of operative, anesthetic, and patient factors have been observed to correlate with the increased risk for development of CPSP. These factors include several biomedical, psychologic, and social predictors significant to predicting the development of CPSP.

**Genetics**

The wide variance of individuals' susceptibility and response to pain can be explained in part by genetic factors. Rat and mice models of CPSP have shown that the risk of developing chronic pain after denervation intervention is heritable (13-15). These studies follow populations of mice or rats that have had peripheral nerve denervation and assess rates of autotomy or self-amputation (an indicator of animal chronic pain) across generations of mice to assess for genetic risk for chronic pain. Hundreds of genes and proteins were identified in the DRG and spinal cord of these rat and mice models (13,16-18).

Similarly in humans, several pain-related genes have been identified as potential direct or indirect contributors to the development of chronic pain (3). Implicated genes including catechol-O-methyltransferase, GTP cyclohydrolase, sodium ion channels, and other tetrahydrobiopterin-related genes have been associated with variability in CPSP susceptibility (3,13,19-21). The role these genes play in complex physiologic changes that occur in CPSP remain poorly elucidated, although recent genetic studies have identified changes in gene expression in over 2,000 genes in chronic pain (22).

In addition to specific genes, clinical conditions such as fibromyalgia syndrome, migraine, burning mouth syndrome, irritable bowel syndrome, irritable bladder, backache, and Raynaud's syndrome have been identified as proxies for increased genetic risk in the development of CPSP after hernia repair and hysterectomy (23-25). A study looking at patients undergoing coronary artery bypass graft with vein harvesting assumed that the sternal and leg surgical sites should have a baseline risk for developing CPSP independent of each other, with the probability of concurrent risk at both sides being some predictable rate of both happening based on independent risk of both surgical sites. However, this study found that the rate of concurrent chronic pain at both surgical sites was higher than predicted if the rate of CPSP at both sites were actually independent, suggesting some genetic predisposition rather than purely a surgical risk factor (26). The genetic influences of CPSP are complex and not yet well understood, but they will be essential in identifying patients who are at risk.

**Psychosocial Factors and Pain Cognition**

Psychosocial factors were not recognized until recently as a significant contributor to the development of CPSP and are only now being targeted by interventions aimed at reducing the risk of CPSP. Factors that have been consistently identified as significant predictors of CPSP development include fear of surgery, fear of pain, anxiety, depression, neuroticism, posttraumatic stress disorder (PTSD), past trauma, and catastrophizing (10,23,27,28). Preoperative fear of surgery in patients has been shown to yield greater pain and diminished quality of recovery, in addition to being associated with heightened levels of postoperative anxiety and depression in populations of patients with breast cancer (27,29). Beliefs regarding pain such as fear of surgery, perceived self-helplessness, and catastrophizing of pain, among other pain cognitions have a greater influence on quality of life than pain intensity, thereby highlighting the importance of considering psychosocial factors in CPSP treatment (30). Further, several studies have shown catastrophizing in patients as a risk factor for the development of CPSP (31-33). In a study of patients who underwent laparoscopic cholecystectomy, patients with persistent postoperative pain were determined to have higher preoperative neuroticism scores compared with those without persistent pain (34). There is a high rate of comorbidity between PTSD and chronic pain, which can be attributed in part to a large overlap of symptoms resulting from common underlying vulnerabilities including anxiety, sensitivity, and other genetic determinants (13,35).

Unlike pain cognitions, psychological factors that have been shown to increase the risk for acute pain do not seem to similarly increase risk for CPSP (23). However, a consistent link between preoperative anxiety and acute postoperative pain has been found, which at its most severe poses a risk factor for CPSP after a variety of operations (36). Psychosocial stressors in patients, especially psychiatric conditions such as depression, are becoming increasingly evidential factors in the development of chronic pain (37). In addition to psychological comorbidities, patients' socioenvironmental condi-
tions such as greater social support and less solicitous responding, meaning reducing the emphasis on the importance of pain from significant others, during the postoperative period have been shown to reduce risk for development of chronic pain (13,31).

There are few studies involving early identification and intervention of patient psychosocial factors in relation to CPSP development. Patients found to have higher levels of optimism and positive emotional state in the perioperative period around breast cancer surgery, coronary artery bypass graft, and total knee arthroplasty have been shown to have had decreased rates of CPSP, which is thought to be related to patient self-efficacy, a patient belief of self-resilience when facing a defined obstacle (22,38-41). Interventions that improve patient optimism and self-efficacy during the perioperative period while targeting psychosocial risk factors afford the most promising treatment of psychosocial stressors associated with CPSP development. Such interventions may include cognitive-behavioral therapy and other interventions that focus on enhancing coping skills (10,22). Recent studies have expanded current understanding of pain cognition and psychosocial factors on the development of CPSP, which will aid in future intervention aimed at addressing these factors.

Preoperative Pain

The presence of preoperative pain is a risk factor for the development of acute and CPSP (27). This risk is thought to arise from nociceptor sensitization within the surgical field and structural changes to the CNS, predisposing sensitization to pain in a patient due to preexisting pain stimuli (42,43). As an example, preoperative pain has been shown to increase the risk of phantom pain in mastectomy and amputations (44,45). Additionally, previous thoracotomy and lower limb amputation in particular have been found to contribute to increased acute postoperative pain and the development of long-term pain (45,46). Identification of patients with existing pain prior to surgery will aid in improved risk stratification and interventions to reduce the risk of developing CPSP.

Operative Factors

There are various aspects of surgical factors that may have been shown to play a role in the development of CPSP. Surgical factors that increase risk of persistent postoperative and chronic pain development include the specific type and location of surgery (mastectomy, thoracotomy, and inguinal herniorrhaphy), duration of surgery (lasting > 3 hours), low volume surgical unit (hospital performing < 60 surgeries compared with > 100 surgeries in high volume breast cancer centers), surgical techniques (pericostal stitches), choice of conventional approach over laparoscopic approach (in hernia and gallbladder surgery), intraoperative nerve damage, and tissue ischemia (10,27,47-49). In thoracotomies and mastectomies, intercostal nerve damage is believed to be a major contributor to chronic neuropathic pain (50). Choice of anterior approach in thoracotomies and mastectomies has been shown to minimize rates of CPSP; this has been thought to be in large part owing to the preservation of the intercostobrachial nerve (51,52). Widespread adoption of minimally invasive surgical approaches, such as use of laparoscopic approach for hernia repair, has reduced rates CPSP (53). Risk for developing chronic pain after laparoscopic hernia repair can be further reduced with the use of lightweight mesh and noninvasive fixation (54). In contrast, concomitant therapies such as radiotherapy and chemotherapy have been shown to contribute to increased risk for CPSP (49,55). Continued identification of surgical factors involved in the development of CPSP is critical.

Anesthesia Technique

The influence of anesthesia on the development of CPSP is relatively unknown. It is thought that anesthesia may play a role in preventing the sensitization of the nervous system that contributes to long-term pain (56). However, halogenated anesthetics are known to contribute to neurogenic inflammation by activating ion channels in the periphery that transmit nociceptive signals, which in itself may contribute to chronic pain development (56). A study conducted on rodents found that the use of ketamine and xylazine, as opposed to barbiturate, for general anesthesia reduced the incidence of neuropathic pain (57). Although there is no consensus, the literature suggests that anesthetic protocols and techniques do play a role in the prevention and development of CPSP, but there remains a need for rigorous studies to guide anesthetic choice.

Postoperative Pain

There is not a distinct transition period between postprocedural pain and CPSP—the mechanisms of the process require further investigation. Studies, however, have found that sustained pain and increased pain sensitivity following certain procedures often extend for months or years. The inflammatory process influencing
the transition from postprocedural pain to chronic pain may be prolonged by surgical factors including insertion of mesh materials and chronic nerve stretching (3). Severe acute postoperative pain has been associated with an increased risk of developing CPSP after various operations including total hip arthroplasty, breast cancer surgery, inguinal herniorrhaphy, caesarean section, and thoracic surgery (55,58-60). There is a strong correlation between acute postoperative pain and CPSP, particularly with thoracotomies due to extensive nerve injury at the surgical site (60-64). Acute surgical pain in the immediate postoperative period is a significant risk factor for developing chronic pain and is a key target for intervention in efforts to reduce the risk of CPSP.

**Predicting CPSP**

The development of accurate predictive models that are able to stratify individual risk for CPSP are critical for the development of targeted preventative interventions. Studies that comprehensively account for the diversity of factors that influence CPSP development in their predictive models are limited. Althaus et al (65) has suggested a risk index using such multifactorial considerations to identify patients at high risk for developing CPSP in patients at a single-center undergoing orthopedic surgery, general surgery, visceral surgery, and neurosurgery. The predictive factors determined include capacity overload, preoperative pain in the operating field, other chronic preoperative pain, postsurgical acute pain, and one or more comorbid stress symptoms, which were used to develop a predictive index (65). This index study presents a promising baseline for the establishment of a generalizable predictive model by showing that risk factors can be used to risk stratify individuals based on easily ascertainable patient factors, although the need to externally validate predictive use remains.

Predictive models are often narrow in the scope of risk factors that they account for, often failing to account for the contribution of surgical factors that have been shown in the literature to contribute to the development of CPSP (66). Other attempts to develop predictive regression models have focused on a cohort of patients receiving a specific surgery. Specifically, a predictive model for the development of CPSP in patients undergoing breast cancer surgery was developed using datasets obtained prospectively and validated on future patients with breast cancer to show predictive value (67). There have been numerous other efforts made to develop regression models for the development of CPSP for surgeries including knee replacement, thoracotomy, and limb amputations, but few make attempts to validate models prospectively and are often underpowered studies that may fail to identify comprehensively all the factors that may contribute to the development of CPSP (68-70).

Because of the novelty of many studies regarding psychosocial contributors to CPSP and lack of universal definition for many such factors, several likely psychosocial risk factors (i.e., depression, anxiety, and catastrophizing) were not accounted for by existing models statistically significant contributors or were not assessed in their relationship to the development of CPSP (65). Psychosocial factors continue to be identified in the literature as significant contributors to the development of CPSP and identified as targets of interventions aimed at reducing the impact and development of CPSP in patients (71).

These initial predictive indices are key to guiding our preventative interventions toward patients who are most at risk for the development of CPSP. These predictive models are the foundation for stratifying patients who are at risk for the development of CPSP, but future studies need to be comprehensive, generalizable, and appropriately powered to identify that the contribution of factors such as genetic predisposition, psychological factors, and type of surgery in addition to the patient factors, such as basic demographics and comorbidities may be significant contributors to risk.

**Preventative Strategies**

**Preventative Analgesia**

Effective management of severe acute pain is thought to be essential in reducing the incidence of CPSP (10). Potential preemptive treatments should be targeted toward limiting and preventing primary afferent stimulation and long-lasting changes in CNS functions. Analgesia aimed at reducing nociceptive stimulation and inflammation leading to primary and secondary sensitization plays an important role in reducing chronic pain development (1). The mainstay of preventative analgesia includes local anesthetic infiltration of the surgical field and judicious titration of opioids to maintain adequate pain control, but now there is an increasing emphasis on multimodal analgesic plans beyond opioids (72,73). The use of opioids can be curtailed with COX-2 inhibitors and nonsteroidal anti-inflamatory drugs (NSAIDs), which are observed to reduce nociceptor transmission in the periphery (74).
Various NSAIDs provide effective analgesia in the CNS and peripheral nervous system during the postoperative period while limiting opioid doses; however, they also have associated adverse effects including perioperative bleeding (72,75). COX-2 inhibitors present an alternative to both NSAIDs and opioids because of their mild adverse effect and tolerability with reduced gastrointestinal side effects, especially gastrointestinal side effects, but still pose cardiac and renal side effects that clinicians must be aware of. In addition to COX-2 inhibition, COX-2 inhibitors prevent the metabolism of endocannabinoid, which has an antinociceptive effect (1,64). The development of an effective preventative approach to CPSP—as opposed to treatment after pain is already established—depends on further study of such multimodal techniques.

**Multimodal Approach**

Perioperative pain presents a significant risk for long-term pain; the development of multimodal analgesic techniques that target the various levels of nociceptive pathways is vital in CPSP prevention and treatment. These techniques work in tandem to reduce the excitability of neurons involved in these nociceptive pathways both centrally with preventative analgesia and peripherally with neuraxial, regional, and local anesthesia (1). The use of adjuncts including ketamine, esmolol, lidocaine, and dexmedetomidine have been shown to be vital in the reduction of both postoperative opioid consumption, and have been shown to reduce risk for the development of CPSP (76,77). Particularly NMDA inactivation with NMDA antagonists such as ketamine, nitrous oxide, and methadone has been shown to be beneficial in the prevention of CPSP (1,8).

Use of adjunct medications such as pregabalin and gabapentin in the perioperative period is thought to reduce surgically induced sensitization and reduce postoperative pain (8,78-80). The benefits of gabapentin and pregabalin may extend to preventing the development of CPSP for specific surgical indications, but when systematically looked at in a Cochrane review there was no significant evidence for preventative effects (81,82). There is continued need for further investigation on the effectiveness of gabapentin and pregabalin for the prevention of CPSP for specific indications given positive outcomes in inguinal hernia repair, knee arthroplasty, and other surgeries (81,83).

Use of local anesthetics may further aid in the prevention of CPSP. During the perioperative period, the use of local anesthesia in the surgical field lessens the severity of acute postoperative pain, and thus may help to lower the risk of CPSP (1). Local anesthesia alone has often failed to show any benefit in reducing the CPSP incidence, as is the case with inguinal surgeries, but when used in tandem with ketorolac, it has been shown to have a reduction in postoperative pain and the development of CPSP (84,85). This presents a promising example of a multimodal approach, but rigorous evaluations of such approaches are limited and must be further explored.

Regional and neuraxial anesthesia can further be used as a tool in the prevention of CPSP. Several studies have shown the beneficial results of regional anesthesia techniques in preventing the development of CPSP thoracotomy, hysterectomy, caesarean section, and iliac crest bone harvesting, with such benefits not seen in other surgery types, possibly owing in part to differing lengths of analgesic treatment (3,58,61,86-89). A 2013 Cochrane review showed that in patients undergoing thoracotomy and breast cancer surgery, development of CPSP can be prevented in one out of every 4 to 5 patients with the use of epidural and paravertebral blocks, respectively (90). The benefits of regional anesthesia have most recently been shown in a 2018 Cochrane review examining nonorthopedic surgeries, exhibiting a reduction in the development of CPSP when reviewing outcomes from randomized control trials in breast surgery, open chest surgery, and caesarean sections (91). The use of regional and neuraxial anesthesia is promising for reducing the risk of CPSP, but the need for further studies examining systematically optimized multimodal protocols remains.

Aggressive multimodal treatment methods should use the combined effects of local, regional anesthesia, and other analgesic medication during the preoperative, intraoperative, and postoperative periods to reduce primary and secondary nociception and sensitization to decrease the incidence of chronic pain development (1,13,92).

**Conclusions**

The underlying pathophysiology in the transition from acute to chronic pain is complex and multifactorial. Repetitive nociception resulting from prolonged inflammatory and neuropathic responses to noxious stimuli causes a cascade of biochemical and structural changes to various pain pathways resulting in sensitization of the peripheral and CNS. Identification of risk factors predisposing patients to CPSP is key to successful targeted interventions. Improving existing risk indices
will be essential in identifying those who are at high risk and will thereby allow clinicians to apply their CPSP-preventative interventions accordingly. Factors such as genetic and psychosocial determinants as well as operative approaches and anesthetic techniques require further study to attain a deeper understanding of the natural history of pain development and progression and its relationship with various risk factors. The tremendous and agonizing impact of CPSP on the quality of life of our patients necessitate the ongoing development of multimodal analgesic treatment and integration of psychosocial interventions and less pain-provoking surgical techniques in future efforts to prevent the development of chronic pain.

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