*Deborah J. Culley, M.D., Editor*

# Persistent Postsurgical Pain

## *Pathophysiology and Preventative Pharmacologic Considerations*

Philippe Richebé, M.D., Ph.D., Xavier Capdevila, M.D., Ph.D., Cyril Rivat, Ph.D.


## ABSTRACT

The development of chronic pain is considered a major complication after surgery. Basic science research in animal models helps us understand the transition from acute to chronic pain by identifying the numerous molecular and cellular changes that occur in the peripheral and central nervous systems. It is now well recognized that inflammation and nerve injury lead to long-term synaptic plasticity that amplifies and also maintains pain signaling, a phenomenon referred to as pain sensitization. In the context of surgery in humans, pain sensitization is both responsible for an increase in postoperative pain *via* the expression of wound hyperalgesia and considered a critical factor for the development of persistent postsurgical pain. Using specific drugs that block the processes of pain sensitization reduces postoperative pain and prevents the development of persistent postoperative pain. This narrative review of the literature describes clinical investigations evaluating different preventative pharmacologic strategies that are routinely used by anesthesiologists in their daily clinical practices for preventing persistent postoperative pain. Nevertheless, further efforts are needed in both basic and clinical science research to identify preclinical models and novel therapeutics targets. There remains a need for more patient numbers in clinical research, for more reliable data, and for the development of the safest and the most effective strategies to limit the incidence of persistent postoperative pain. **(ANESTHESIOLOGY 2018; 129:590-607)**


MORE than 100 million people in the United States and Europe and 312 million worldwide undergo surgical procedures each year.[1] The number of surgical procedures increased 34% between 2004 and 2012.[1] These numbers are expected to grow in all economic environments as the elderly population, which is overrepresented among surgical populations, continues to grow worldwide. Complete clinical recovery without complications is important to patients. Pain caused by surgical procedures remains a significant clinical problem that seriously impacts postoperative rehabilitation and health-related quality of life. Despite increased preclinical and clinical research on the pathophysiology of postoperative pain and recent advances in analgesic therapies, many patients still complain about severe acute postoperative pain and feel they did not receive adequate postoperative analgesia. Recently, Fletcher *et al.*[2] reported that every 10% increase in the time spent in severe postoperative pain was associated with a 30% increase in chronic pain 12 months after surgery. Authors also reported that acute postoperative pain is a predictive factor for chronic pain after hernia repair, sternotomy, knee replacement, and limb amputation.[3–5] The development of chronic pain after surgery, also called persistent postoperative pain, is recognized as a significant health problem affecting the postoperative outcome of patients, their rehabilitation, and their quality of life with important legal and medicoeconomic consequences. Persistent postoperative pain has been defined by the International Association for the Study of Pain as a clinical discomfort that lasts more than 2 months postsurgery without other causes of pain such as chronic infection or pain from a chronic condition preceding the surgery.[6] According to the International Classification of Diseases,[7] persistent postoperative pain has greater intensity or different pain characteristics than preoperative pain and is a continuum of acute postoperative pain that may develop after an asymptomatic period. International Classification of Diseases defines the duration for persistent postoperative pain at 3 months postsurgery because healing times differ among different procedures.

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 399.

Submitted for publication February 1, 2017. Accepted for publication March 30, 2018. From the Department of Anesthesiology and Pain Medicine, University of Montreal, Maisonneuve-Rosemont Hospital, Montreal, Quebec, Canada (P.R.); Department of Anesthesiology and Critical Care Medicine, Lapeyronie University Hospital, Montpellier, France (X.C.); National Institute of Health and Medical Research, Unit 1051, Institute for Neurosciences of Montpellier, Montpellier, France (X.C., C.R.); and the Department of Biology-Health, University of Montpellier, Montpellier, France (X.C., C.R.).

 Anesthesiology 2018; 129:590–607




<zdoi;10.1097/ALN.0000000000002258>

Table 1. Incidence of Persistent Postsurgical Pain according to Surgical Procedure

| Surgery | Moderate to Severe Pain beyond 3 Months |
|---|---|
| Amputation[94] | 30 to 81% |
| Cesarean section[178] | 15.4% |
| Cholecystectomy[17] | 3 to 56% |
| Hernia repair[8] | 5 to 35% |
| Hysterectomy[179] | 5 to 32% |
| Mastectomy[8] | 20 to 50% |
| Hip replacement[180] | 7 to 23% |
| Thoracotomy[17] | 61 to 70% |

Table 1 shows that the incidence of both acute postsurgical pain and persistent postoperative pain varies across individuals and procedures. What is clear is that as many as 20 to 56% of patients develop chronic pain after surgery.[8,9] In a study that evaluated[2] persistent postoperative pain at 12 months after surgery, the incidence of moderate to severe persistent postoperative pain was 11.8% (95% CI, 9.7 to 13.9), the incidence of severe pain (numerical rating scale greater than or equal to 6) was 2.2% (95% CI, 1.2 to 3.3), and signs of neuropathic pain were recorded in 35.4 to 57.1% of patients with persistent postoperative pain. Patients may develop persistent postoperative pain after "common surgical procedures" including amputation, breast surgery, thoracotomy, inguinal hernia repair, coronary artery bypass, and caesarean section. Among surgical patients, 2 to 10% have persistent severe chronic pain (pain greater than 5 on a visual analogue scale up to 10) at 6 months postsurgery.[8,10–14] Nevertheless, how persistent postoperative pain is variously defined and described may play a role in the variability of the reported incidence. In 2012, Schug[15] reported a reduction from 40 to 18% in the prevalence of persistent postoperative pain when only moderate or severe pain in the area of surgery was taken into consideration (numerical rating scale more than 3 of 10). However, when Schug excluded patients who had pain in the area of surgery before the operation, the prevalence of persistent postoperative pain fell to 6%. Persistent postoperative pain affects millions of patients every year; it is a potential burden for the healthcare systems that until recently has been an unrecognized complication of surgery. What we can do to prevent patients from developing chronic pain postsurgery is now considered one of the most important research priorities in anesthesia and perioperative medicine.[16]

The major objective of this review is to provide both a conceptual view of the transition from acute pain to persistent postoperative pain from a neurobiological perspective and an updated pragmatic review of the pharmacologic strategies that can be used to prevent the development of persistent postoperative pain. Here we describe both the basic science mechanisms of acute pain and the critical factors that may be responsible for transition from acute pain to persistent postoperative pain. In the second part, we provide the various pharmacologic strategies for limiting the risk of pain chronification postsurgery. Our research focused mainly on published clinical studies and meta-analyses evaluating the effects of clinically available drugs that can demonstrate preventative effects on the development of persistent postoperative pain. We also considered drugs commonly used by anesthesiologists that may be of interest in preventing persistent postoperative pain due to their mechanism of action even without or with small reported clinical evidence.

## Understanding the Complexity of the Transition from Acute to Persistent Postoperative Pain

The transition from acute to persistent postoperative pain is a complex and poorly understood progressive process involving biologic, psychologic, and socioenvironmental factors.[17] Animal studies have helped identify the neurobiological foundation of surgery-induced pain sensitization. Here, the literature review is selective rather than exhaustive. Due to the important number of relevant publications and a recent review describing the pathophysiology of postoperative pain,[18] this review focuses mainly on the most relevant advances on the pathophysiology of surgery-related animal models and on the transition from acute to chronic postsurgery pain.

### *Preclinical Findings on Postoperative Pain Sensitization*

Various animal models have been developed to better understand the pathophysiology of postoperative pain. The incisional pain model developed by Brennan *et al.*[19] and Pogatzki-Zahn *et al.*[20] demonstrated that postincisional nociception produces cellular and molecular alterations that are distinct from other pain models. It is well acknowledged that pain after surgery is a very specific entity that is not an inflammatory response alone or isolated nerve injuries but is usually a combination of both, even if pain after surgery does not often involve nerve injury.[21] It is clear that the intensity of pain produced by tissue injury is related to two components. The first is directly related to the intensity of nociceptive inputs resulting from incision (see Pogatzki-Zahn *et al.*[18]). The second is specifically supported by mechanisms of peripheral and central sensitization that enhance the postincisional pain sensation for a given nociceptive input level (fig. 1).

**Peripheral Sensitization.** After incision of the skin and muscle, several gene changes in the primary afferent sensory neurons of the dorsal root ganglia are described in a time-dependent manner that persist long after the surgical incision. These factors affect nociceptor activation and influence tissue remodeling, wound healing, reinnervation, and the immune response, depending on the tissue.[22] Among these different factors, gene expression of artemin and nerve growth factor were increased in both incised skin and muscle. These data are in agreement with another report showing that nerve growth factor is present adjacent to the incision and localized in Schwann cells and axons.[23] Several reports demonstrated the importance of local nerve growth factor in the

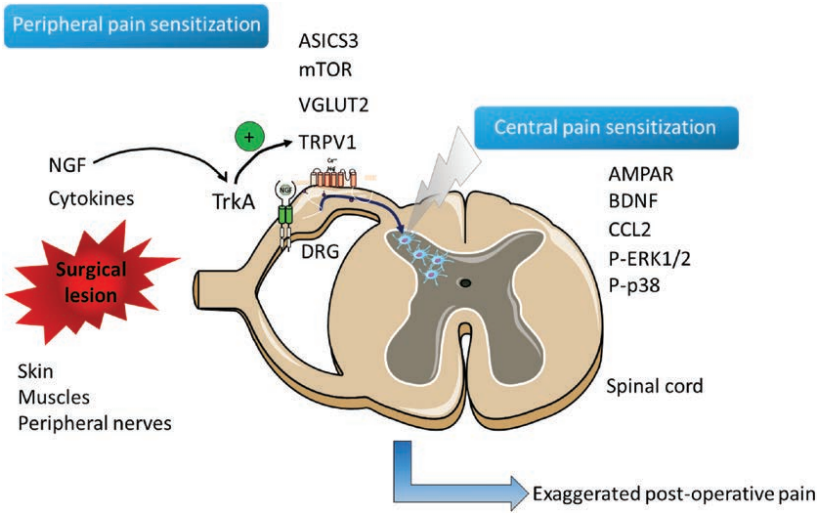


**Fig. 1.** Summary of the mechanisms that may support pain sensitization after surgery leading to persistent postsurgical pain. Nociceptive inputs due to surgery produce local molecular changes such as nerve growth factor (NGF) and cytokine release and in primary sensory neurons of the dorsal root ganglia (DRG) including increased expression of acid-sensing ion channels 3 (ASICS3), transient receptor potential cation channel subfamily V member 1 (TRPV1), and mechanistic target of rapamycin (mTOR). The latter controls vesicular glutamate transporter 2 (VGLUT2) expression that generates an increased glutamatergic activity in the spinal cord. These changes are responsible for peripheral pain sensitization that then influences spinal neuronal activity referred to as central pain sensitization. Central sensitization depends upon increased expression of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and brain-derived neurotrophic factor (BDNF) release. Activation of AMPAR may account for extracellular signal–regulated kinase 1/2 activation (P-ERK1/2) leading to the development of sustained pain hypersensitivity. MAPK kinase p38 activation (P-p38) and chemokine ligand 2 (CCL2) also contribute to surgery-induced central pain sensitization. TrkA = tropomyosin receptor kinase A.

development of pain hypersensitivity, making nerve growth factor one of the critical factors in the initiation of peripheral sensitization leading to subsequent postincisional persistent pain.[24–27] Nerve growth factor, *via* its receptor tropomyosin receptor kinase A, was shown to activate the mitogen-activated protein kinase p38 in the dorsal root ganglia, increasing by a transcriptional mechanism the expression of the transient receptor potential cation channel subfamily V member 1 in the free ending fibers rendering the animals hypersensitive to heat stimuli.[28] In addition to nerve growth factor, local cytokines, the most important being interleukin 1β and the chemokine (C-X-C motif) ligand 1, have also been implicated in the pathophysiology of incisional pain and are controlled by substance P receptor.[24] Peripheral sensitization also includes changes in ionotropic channel expression in sensory neurons such as acid-sensing ion channel 3. Its blockade with the specific sea anemone toxin APETx2 reduced postincisional pain-related behavior.[29] In addition, the serine–threonine protein kinase, mechanistic target of rapamycin located in the dorsal root ganglia, has been implicated in maintenance of thermal hyperalgesia 3 days after the incision.[30] Of note, the mechanistic target of rapamycin controls the expression of the vesicular glutamate transporter 2 that loads glutamate into synaptic vesicles and controls glutamatergic synaptic activity.[30] The activation of the mechanistic target of rapamycin may represent an important event in initiating central pain sensitization that is known to be glutamate-dependent. Altogether, peripheral changes may facilitate sustained activation of primary afferent neurons that generate primary hyperalgesia and lead to subsequent neuroplastic changes supporting the development of central sensitization.

**Spinal Central Sensitization.** Central sensitization is a type of long-term adaptive neuroplasticity that amplifies pain signaling by affecting neurons in the spinal cord, resulting in a form of "pain memory." The mechanisms involved are similar to those implicated in hippocampal long-term potentiation.[31] Central sensitization is mainly responsible for secondary hyperalgesia, which is defined as increased pain sensitivity outside the area of injury. Pain sensitization that is dependent on glutamate *via* $Ca^{2+}$-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptors has been implicated in the development of pain hypersensitivity after incision (see Pogatzki-Zahn *et al.*[18]). Other factors have been shown to be increased after surgery with a positive impact on pain sensitization. Brain-derived neurotrophic factor from primary nerve terminals increased in the dorsal horn of the spinal cord plays a crucial role in mechanical allodynia after incision.[32] Brain-derived neurotrophic factor increase along with the activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptors may account for the activation of extracellular signal–regulated kinases 1 and 2 that regulate incision-induced pain hypersensitivity.[33] Interestingly, in addition to the implication of neuronal mechanisms, some studies suggest the importance of glial signaling in spinal nociceptive sensitization after plantar incision.[24,34–36] Glial signaling, especially microglia activation,

has been linked to chemokine ligand 2.[37] Activation of the mitogen-activated protein kinase p38 in microglia was shown to support in a time-dependent manner the severity of postincisional pain hypersensitivity in rodents.[37,38] Notably, the mechanisms of pain sensitization can be modulated by clinically relevant factors (fig. 2).

### Opioids and Stress Influence Pain Sensitization Induced by Incision

**Opioid-induced Hyperalgesia in Rodents.** Patients who undergo surgery receive either general or local anesthesia to oppose the negative consequences, especially surgery-produced pain. Based on this idea, we developed an animal model combining high-dose opioids administered coincident with the incision of one hind paw. In this context, it has been shown that fentanyl produces analgesia as expected but exaggerates postoperative pain hypersensitivity.[39,40] Similar results were obtained after remifentanil administration.[41,42] This phenomenon is referred to as opioid-induced hyperalgesia. Several animal studies emphasize the potential role of high-dose opioids in the exaggeration of postoperative pain (reviewed by Angst and Clark[43]). Opioid-induced hyperalgesia was dose- and time-exposure–dependent. Different animal studies also demonstrated that morphine treatment given before incision dramatically prolongs subsequent pain hypersensitivity produced by hind paw incision.[44] The mechanisms for the neuroplastic changes induced by acute or sustained opioid administration have recently been reviewed (fig. 2).[45,46] High doses of opioids administered coincident with the incision of one hind paw may facilitate pain sensitization produced by the surgery *via* the implication of *N*-methyl-D-aspartate (NMDA) receptors[47] and may activate glial cells.[48] The enhancement of pain hypersensitivity observed in morphine-treated animals has been related to an increase in p38 and extracellular signal–regulated kinase activation in the dorsal spinal cord.[49] These data suggest that opioids may facilitate the development of persistent postoperative pain in rodent.

**Periincisional Stress Can Influence Central Pain Sensitization.** Recently, it was proposed that short-term preincisional stress can also have a negative impact on the intensity and the duration of pain hypersensitivity developed after plantar incision. This is linked to the activity of the hypothalamic–pituitary–adrenal axis, because blocking the spinal glucocorticoids receptor or removing adrenal glands completely prevents the effects of periincisional stress on incision-induced pain hypersensitivity.[50] To go further into the mechanisms, it was reported that stress appears to regulate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptor phosphorylation and trafficking. This leads to a change in synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptor subunit composition associated with the activation of $Ca^{2+}$-dependent protein kinases, thereby promoting α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptor phosphorylation and other phosphorylation-triggered activities.[51] This positive feedback loop may contribute to the molecular mechanisms that underlie preincisional stress-induced persistent pain after incision (fig. 2).

**Summary of Incision-induced Pain Sensitization.** Complex mechanisms triggered by the surgical insult underlie the development of acute postoperative pain that in turn may produce sustained changes in nociceptive pathways. Peripheral changes can be exemplified by the transcriptional and posttranslational changes that occur in the primary sensory neurons in the dorsal root ganglia. They are promoted by the activation of neurotrophin receptors such as tropomyosin receptor kinase A. This results in the release of glutamate in the dorsal horn of the spinal cord leading to the long-term activity of spinal secondary afferent neurons responsible for the so-called central sensitization that is highly dependent upon the activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptors (fig. 1). All of these changes can be influenced by opioid and stress that may contribute to the development of persistent postoperative pain (fig. 2).

### Long-lasting Neuroplastic Changes after Incision

Several animal studies reported that an initial nociceptive insult may actually sensitize individuals to pain for a very long time, even if pain behavior wears off. That means that even if postoperative pain resolves in most of the patients, surgery may sensitize patients to subsequent nociceptive stimuli. To explain this phenomenon, it has been proposed that animals with previous injury did not return to their initial pain state but are in a new biologic state associated with a high-level balance between opioid-dependent analgesic systems and pronociceptive systems that masked one another.[52] This is in agreement with the compensatory response hypothesis supported by the opponent process theory[53] as demonstrated by the capacity of the opioid antagonist naloxone to precipitate robust hyperalgesia after the resolution of the pain hypersensitivity produced by tissue injury (carrageenan, incision, complete Freund's adjuvant) but no change in basal nociceptive threshold in naïve animals. This suggests that tissue injury activates pain inhibitory systems to limit the intensity and duration of pain hypersensitivity associated with incision. The recruitment of the pain inhibitory system occurs progressively after the injury at the periphery shown by the increased expression in the skin of proopiomelanocortin and Oprm1-encoding μ-opioid receptors, both of which remain elevated up to 3 days.[54] Of note, opioid activity also takes place in the central nervous system as evidenced by a micro positron emission tomography imaging animal study.[55] A study by Corder *et al.*[56] further examined the implication of the endogenous central opioid system after inflammatory pain. They first showed that inflammation produced constitutive activation of μ-opioid receptors that repressed spinal nociceptive signaling for months and that opioid antagonist-precipitated hyperalgesia is blocked

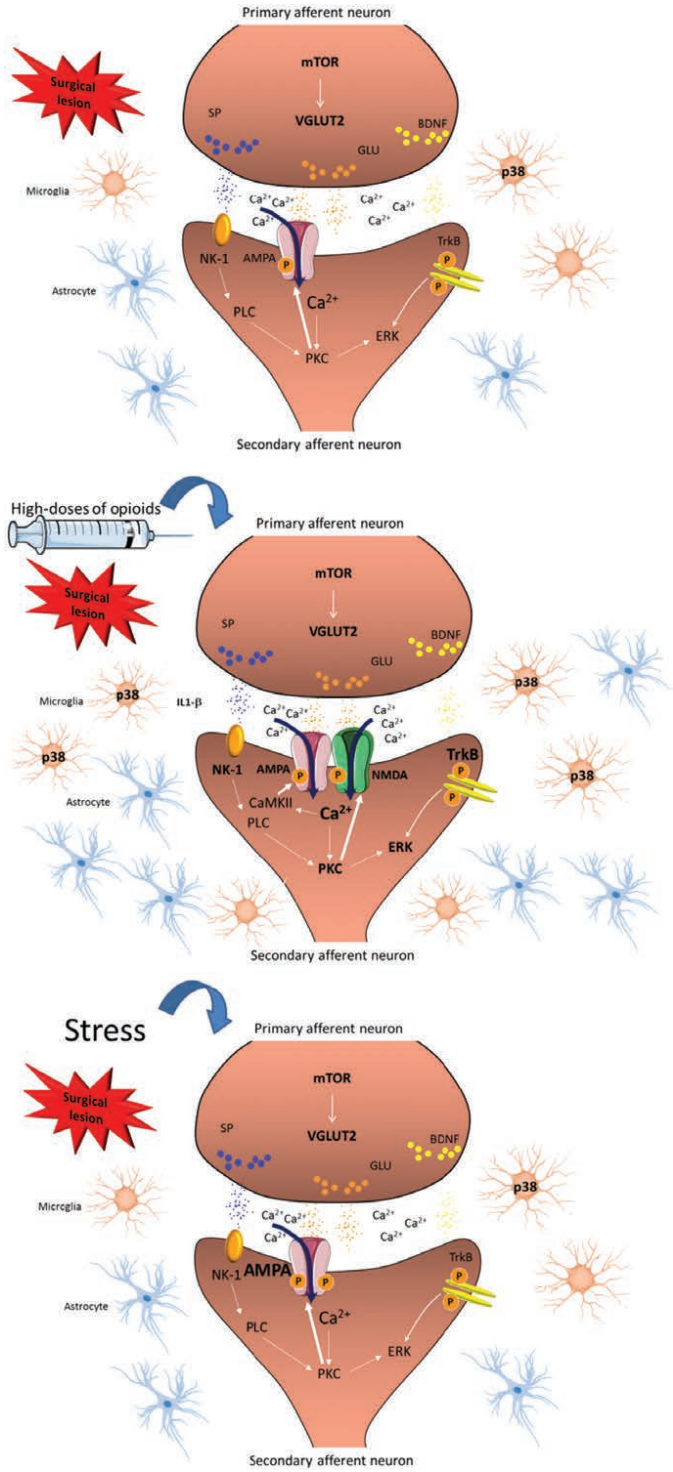


**Fig. 2.** Facilitation of central pain sensitization by opioids and stress after surgery. Surgery induces $Ca^{2+}$ α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-dependent and glial (microglia and astrocytes) central pain sensitization. Microglia activation *via* p38 activation represents also an important factor in incision-induced pain sensitization. High doses of opioids have been shown to produce pain hypersensitivity *via* activation of the *N*-methyl-D-aspartate (NMDA) receptors, overactivation of brain-derived neurotrophic factor (BDNF) receptor tropomyosin receptor kinase B (TrkB), increased content of substance P (SP), and glial activation. Thus, perioperative doses of opioids may overactivate pain sensitization processes (*bold characters*). In addition, preoperative opioid administration might increase the risk of developing postsurgical pain *via* the activation of p38 in microglia and the release of cytokines such as interleukin 1β (IL-1β). Central pain sensitization induced by surgery may be also increased by perioperative stress *via* an enhanced expression of AMPA receptor (bold characters). As a consequence, activation of $Ca^{2+}$-dependent kinase might be activated leading to long-lasting neuronal hyperexcitability. CaMKII = calmodulin kinase II; ERK = extracellular signal–regulated kinase; GLU = glutamate; mTOR = mechanistic target of rapamycin; NK1 = neurokinin 1 receptor; PKC = protein kinase C; PLC = phospho lipase C; VGLUT2 = vesicular glutamate transporter 2.

by the inactivation of the adenylate cyclase AC1, suggesting that withdrawal from tonic endogenous μ-opioid receptor activity produces pain hypersensitivity *via* adenylate cyclase AC1 superactivation. δ-Opioid receptors and their ligand dynorphin are also involved in the compensatory response triggered by incision.[57]

Clinical evidence for naloxone-induced latent pain sensitization was recently found in human volunteers.[58] Although this study involved only a small number of volunteers, this preliminary study reported a large heterogeneity in the naloxone response, suggesting individual differences in the development of the opioid adaptive response.

Collectively, these data demonstrate that it is the adaptive response occurring after surgery that provides a natural recovery after acute pain. The opioid-dependent adaptive response triggered by tissue injury pertains to an important conceptual advance called allostasis, the active process by which the body responds to daily events and maintains homeostasis.[59] Allostatis has been associated with the terms "allostatic load" and "overload" to refer to the wear and tear that results from either exaggerated stress or from inefficient management of allostasis.[60] In the context of postincisional pain, the adaptive response observed after incision reflects the allostasic load that unmasks the sustained activation of pronociceptive systems. The role of this plasticity may be to protect against permanent damages produced by tissue injury. However, it may enhance vulnerability to subsequent painful stimuli or nonpainful stimuli such as stress. Indeed, animal studies report that nonpainful environmental stress produced pain hypersensitivity in animals that were exposed to acute pain,[61] especially when they had been treated with high doses of opioids. This suggests that acute pain may produce pain vulnerability due to persistent pain sensitization placing the individuals at risk for developing persistent postoperative pain (fig. 3). This has been referred to as latent pain sensitization presented as secondary outcomes in several studies.[39–42]

The concept of latent pain sensitization provides an interesting view on how patients can develop persistent pain after surgery. The importance of such an adaptive response in controlling the development of persistent postoperative pain can be illustrated by those suffering from congenital insensitivity to pain due to the deletion of Nav1.7 gene. Administration of naloxone in one human with congenital insensitivity to pain reverses analgesia, making the subject able to detect a single noxious heat stimulus in the presence of naloxone.[62] Thus, the inability to engage tonic pain inhibitory systems associated with persistent pain sensitization are likely to be fundamental factors that together contribute to the initiation and the maintenance of chronic pain after surgery because endogenous analgesia seems to reflect the individual's ability to manage down noxious events (fig. 3). To illustrate this point, it has been shown that efficient endogenous analgesia evaluated by diffuse noxious inhibitory control activity or newly called conditioned pain modulation is correlated with lower risk of developing chronic postthoracotomy pain.[63] This observation can be related to an animal study by De Felice *et al.*[64] that demonstrates the importance of the engagement of descending pain inhibitory systems from the rostral ventromedial medulla to oppose the development of chronic pain after ligation of the sciatic nerve. Based on this conceptual advance, we can understand why the evaluation of preoperative endogenous analgesia can be used to predict the development of pain disorders after surgery in humans,[65] although other articles failed to report an association between preoperative conditioned pain modulation and the development of persistent postoperative pain after funnel chest repair.[66]

### Mechanisms Supporting Persistent Pain Sensitization after Incision

The phenomenon of persistent pain sensitization produced by surgery remains poorly understood; further investigations will be necessary to understand the underlying mechanisms. NMDA receptors seem to play a critical role in the establishment of long-term pain vulnerability because their blockade completely neutralizes the so-called stress-induced hyperalgesia in animals treated with high doses of opioid.[61] Interestingly, glial activation has also been implicated in the long-lasting pain sensitization induced by plantar incision.[67] Recently, a model of incision that did not involve damage to the gross peripheral nerves was developed to address the etiological factors of long-term sensitization produced by surgery.[68] The data showed that incision produced an increased expression in the dorsal root ganglia of the neuronal stress markers activating transcription factor 3 and neuropeptide Y up to 28 days after the surgery, whereas calcium/calmodulin-dependent protein kinase IV and isolectin B4 binding were decreased. These observations confirm that tissue damage is able to induce long-lasting changes in the expression of genes related to stress/tissue damage beyond tissue healing.

A model called "hyperalgesic priming,"[69] in which a previous injury induced a prolonged period of susceptibility to exaggerated sensitization after subsequent injury, is classically used to study the neuroplasticity underlying persistent pain sensitization. The model consisted of performing an initial surgery. Persistent sensitization of nociceptive pathways was revealed by subsequent challenges with the administration of prostaglandin E2. In this model, the animals that underwent a plantar incision developed exaggerated pain hypersensitivity after prostaglandin E2 administration 15 days after the incision.[70,71] It was shown that the protein kinase Mζ, known to play a critical role in the induction of long-term potentiation, is involved in the maintenance of persistent nociceptive sensitization after plantar incision.[70,72] Most importantly, emerging evidence suggests the involvement of epigenetic processes in the regulation of persistent functional changes in the nervous system including pain transmission. Epigenetics refers to the processes that govern trait variations without changes in the genomic DNA sequence. DNA is tightly wound around proteins called histones, forming

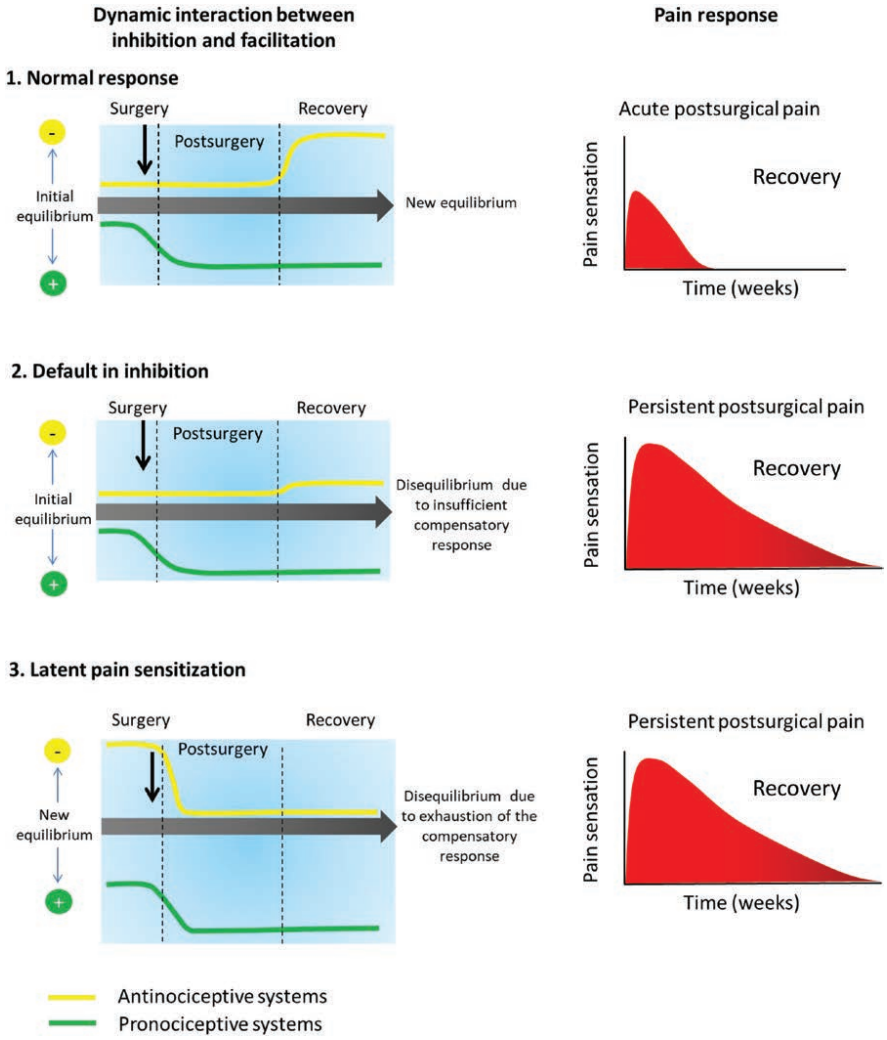


**Fig. 3.** Schematic view of the development of persistent postsurgical pain *via* the engagement of pronociceptive and antinociceptive systems. Point 1: In normal conditions, initial equilibrium represents a low-level balance between the pronociceptive and antinociceptive systems. In these conditions, surgery produces disequilibrium *via* the sustained activation of pronociceptive systems (pain sensitization). This promotes hyperalgesia and allodynia, which wear off (recovery) due to the recruitment of antinociceptive systems (acute postsurgical pain). This leads to the establishment of a new equilibrium (allostatic state) that may represent increased vulnerability to developing persistent postsurgical pain (point 3). Point 2: Default in the recruitment of antinociceptive systems (pain inhibition) postsurgery may account for the maintenance of hyperalgesia and/or allodynia and potentially for the development of persistent postsurgical pain. Point 3: Before surgery, pain vulnerability is associated with a new equilibrium that represents a high-level balance between the pronociceptive and antinociceptive systems. In these conditions, surgery may sensitize the activation of pronociceptive systems leading to an important disequilibrium between both systems. As a result, exaggerated hyperalgesia may be observed. This may lead to the exhaustion of the antinociceptive systems. Hence, the absence of tonic pain inhibition results in the maintenance of hyperalgesia/allodynia participating in the development of persistent postsurgical pain.

a complex known as chromatin. Recent evidence demonstrates that a histone acetyltransferases inhibitor partially blocks latent pain sensitization as revealed by the reduction of exaggerated pain hypersensitivity induced by prostaglandin E2 intrathecal injection.[54] Epigenetic alteration seems to affect the chemokine receptor CXCR2 signaling pathways in the spinal cord that control exaggerated incisional mechanical hypersensitivity.[71] Thus, epigenetic mechanisms are important factors in the transition from acute to chronic pain after incision.[73] They seem to explain many facets of acute and chronic pain susceptibility.[74]

### Summary of Surgery-induced Persistent Pain Sensitization

Pain sensitization can be maintained for very long periods by processes involving epigenetic changes, resulting in a long-lasting state of pain vulnerability (allostatic state). Such processes may represent steps toward persistent postoperative pain. Endogenous adaptation depending on increased endogenous opioid activity may limit the incidence of persistent postoperative pain. The inability to recruit these endogenous pain inhibitory systems may result in the development of persistent postoperative pain (fig. 3).

## Risk Factors for Developing Persistent Postoperative Pain

Because important reviews already discuss the different factors that may contribute to the development of persistent postoperative pain,[75] this topic is not developed in our review. Here we briefly mention the most important factors that are classified as follows.

### *Preoperative Factors*

**Preexisting Pain.** Some studies reported that pain, current or past, before the surgery may influence the resolution of postoperative pain by increasing the duration of recovery,[9,76] thus favoring the development of persistent postoperative pain. Amputees are the best example of this phenomenon.[12] However, the severity of preoperative pain seems to be associated with persistent postoperative pain, regardless of the type of surgery.[9,76] The description of the long-term pain sensitization produced by tissue injury may explain the influence of preexisting pain on the persistent postoperative pain. Therefore, patients with history of repeated surgeries may require particular attention for the prevention of persistent postoperative pain.

**Preoperative Opioid Exposure.** Patients who undergo surgery are often treated with pain reduction therapies, especially opioids. Patients that chronically take opioids may require three to four times the amount of opioids administered to patients that are opioid-naïve. These observations strongly suggest that opioid exposure may facilitate the risk of developing persistent postoperative pain. Several studies or reviews reported the impact of preoperative opioid consumption on postoperative pain and outcomes.[77,78] For instance, Keller *et al.*[79] showed that 48% of those taking opioids before thoracotomy had chronic postthoracotomy pain, compared with 5% of those not taking opioids.

**Genetics.** This represents an interesting field of investigation that could allow the identification of patients at risk for developing persistent postoperative pain. Some polymorphisms have been associated with variable pain sensitivity or opioid response. This is the case for catecholamine-*O*-methyltransferase polymorphism and melanocortin-1 receptor gene polymorphism in red-haired women that are associated with higher response to opioids.[80] However, in a recent study evaluating the association between persistent postoperative pain and 90 genetic markers after different types of surgery, no difference was observed between patients with persistent postoperative pain and controls.[9] Future investigations are necessary to determine whether or not gene variants can be related to the risk of developing persistent postoperative pain. As emphasized by Mogil,[81] the challenge in this field is quite enormous.

**Psychologic Factors.** A review by Hinrichs-Rocker *et al.*[82] focused on the psychologic factors that can influence the development of persistent postoperative pain. In general, anxiety, depression, fear of surgery and postoperative pain, catastrophizing (tendency to exaggerated pessimism about outcome), lack of support in the patient's environment, and general level of stress are factors that contribute to or influence the development of persistent postoperative pain.[10,83] Stress-induced pain sensitization can explain the influence of psychologic factors on the development of persistent postoperative pain. Cognitive functions such as attention, visual memories, and executive function have also been linked to a greater risk of developing persistent postoperative pain after surgery.[84]

**Preoperative Pain Questionnaires and Quantitative Sensory Testing.** Overall, it has been proposed that pain questionnaires or exaggerated responses to experimental stimuli (quantitative sensory testing) may be useful in identifying patients with a higher risk of developing persistent postsurgical pain, but the correlation remains controversial.[85] These questionnaires, as well as the quantitative sensory testings, are time-consuming and most often difficult to perform. This is particularly true in the daily clinical context when the anesthesiologist meets his patient for the first time on the day of the surgery.[86,87] Also, recent studies pointed out that using perioperative pain trajectories constructed from a patient's diary might identify patients at risk of developing persistent postoperative pain. Such screening and patient phenotyping would potentially allow preventative strategies to oppose the development of persistent postoperative pain.[88] Moreover, in most countries worldwide, anesthesiologists do not have the chance to see their patients before the day of the surgery. Patients' files are screened at the preoperative clinic by nurses, and very few of the patients see an anesthesiologist in person. Thus, most often, anesthesiologists discover the schedule and the patients on the morning of the surgery, and this makes it hard to develop a strong strategy to act on risk factors such as anxiety or catastrophizing cited above.

### *Postoperative Factors*

**Intensity of Acute Postoperative Pain.** As described above, pain sensitization is defined as "a form of synaptic plasticity in dorsal root ganglia and the spinal cord that amplifies pain signaling"[31] and finds its origin in perioperative noxious and surgical stimuli and inflammatory mediators and glial activation.[31,48,89] When identified after surgery, this pain sensitization translates into clinical hyperalgesia that is associated with a higher risk of developing persistent postoperative pain.[31,48,89–91] High postoperative pain intensity[92–94] is one of the most important factors along with the size of the hyperalgesic or allodynic area around the surgical incision. The importance of the latter parameter has been clinically determined after colonic, gynecological, and kidney surgeries, showing the relationship between the area of secondary punctuate hyperalgesia and the presence of persistent pain 3 to 6 months after the surgery.[95–99]

**Nerve Injury due to the Surgery.** Several clinical reports emphasize nerve damage during surgery as one of the main factors of chronic postoperative pain.[100] Nerve injury is associated with numerous molecular and cellular changes

including neuroimmune interaction causing heightened excitability of the primary afferent neurons.[101,102] The pain sensitization is then propagated to the spinal cord along with an increased synaptic transmission and plasticity up to the spinal cord and the brain.[103] Very recently a "nerve injury-induced neuropathic pain probability grading system" has been used to identify surgeries at high risk of developing neuropathic pain.[21] Neuropathic pain prevalence is 65% in thoracic and breast surgeries, 31% in groin hernia repair, and 6% in orthopedic surgeries like total hip or knee arthroplasty. However, many patients with peripheral nerve injuries do not develop persistent pain. For instance, development of chronic neuropathic pain after traumatic nerve injury occurs in less than 5% of individuals,[104] and this variability is likely a consequence of recruiting endogenous pain inhibitory systems arising from the central nervous system.[63]

### *Other Risk Factors That Should Be Further Considered*

**Immune Activity.** Relationships between inflammation, single-cell immune signature and clinical parameters of surgical recovery, including functional impairment and pain chronification, have been recently reported in some clinical studies.[105–108] Signal transducer and activator of transcription 3, and the transcription factor nuclear factor- κB pre- or postoperative signaling responses in subsets of cluster of differentiation 14+ monocytes are related to poor patient outcome. These data are in agreement with basic science reports showing the importance of neuroimmune interaction in the development of pain sensitization and consequently of persistent postoperative pain. They suggest that inflammatory response *via* the recruitment of monocytes represents an important risk factor for postoperative complication that may include persistent postoperative pain.

**Perioperative High Doses of Remifentanil.** Although controversial, multiple clinical trials demonstrate that opioid-induced hyperalgesia is common after surgery.[43,109–112] Opioid administration during surgery may activate NMDA receptors and/or glial cells resulting in higher pain scores, higher opioid consumption, and higher postoperative acute hyperalgesia, although the link between high doses of intraoperative opioids and the development of persistent postoperative pain is limited to a few studies.[109,113] The first identified a correlation between high intraoperative remifentanil dosages with a higher incidence of persistent postoperative pain up to 1 yr after cardiac surgery[114]; the second identified a higher incidence of persistent postoperative pain up to 1 yr after thoracic surgery when high intraoperative dosages of remifentanil were administered when compared to epidural.[111] Improving our understanding on opioid-induced hyperalgesia will improve postoperative management and potentially decrease the risk of chronic pain postsurgery. However, large, prospective, randomized, multicenter trials have not been performed to determine whether there is a relationship between high intraoperative opioid dosing and whether that might lead to an increased risk of developing persistent postoperative pain.

## Pharmacologic Prevention of Persistent Postoperative Pain

### *Antiinflammatory Drugs*

**Cyclooxygenase-1 and Cyclooxygenase-2 Inhibitors.** Nonsteroidal antiinflammatory drugs inhibit spinal and peripheral cyclooxygenases enzymes, whereas acetaminophen might inhibit central cyclooxygenase transcription.[115] Nonsteroidal antiinflammatory drugs and acetaminophen are part of the multimodal perioperative pain management strategy. Although there is no doubt that perioperative multimodal analgesia is beneficial for acute pain management, there is no strong evidence that these medications prevent persistent postoperative pain.

**Corticosteroids.** Inflammation associated with tissue injury leading to peripheral and central sensitization can be targeted by corticosteroid therapy. However, administration of glucocorticoids is controversial due to both their effect on the hypothalamic–pituitary–adrenal axis and evidence that decreased hypothalamic–pituitary–adrenal axis activity is associated with poor outcomes after disc surgery.[116] Although it is common to administer 4 to 8 mg of intravenous dexamethasone to decrease and prevent postoperative nausea and vomiting[117] and although acute postoperative pain has been shown to be reduced when IV dexamethasone 4 to 20 mg is used intraoperatively,[118,119] there is no evidence in humans that glucocorticoids administration reduces the risk of developing persistent postoperative pain.[120,121] Preclinical data suggest that glucocorticoid administration may facilitate central pain sensitization (see section on stress-induced pain sensitization). To conclude, further investigation will be necessary to reconcile preclinical and clinical findings regarding the use of corticosteroids.

### *Regional Anesthesia and Local Anesthetics*

The role regional anesthesia on the incidence of persistent postoperative pain is frequently debated, although there is hope that regional anesthesia may reduce the incidence of persistent postoperative pain by a number of different mechanisms.[12,97,99,122–128] Preexisting factors such as pain, inflammation, or preoperative opioid exposure could explain these controversies. Regional anesthesia might be able to reduce the incidence of persistent postoperative pain by different mechanisms.[129]

A continuous or long-lasting nerve block can block transmission of nociceptive and inflammatory input induced from the periphery to the central nervous system,[130,131] and local anesthetics themselves may limit neuronal inflammation and activation of glial cells[132,133] that may limit the development of persistent postoperative pain. In addition, regional anesthesia is associated with a significant reduction in the use of intraoperative opioids that may decrease opioid-induced hyperalgesia, although the beneficial effect of regional anesthesia is lost when very high or repeated doses of opioids are administered in the perioperative period.[134,135]

**Epidural Analgesia.** Perioperative epidural anesthesia has been documented to reduce the risk of persistent pain, although only when the epidural is used both intra- and postoperatively.[97,111,136] A recent meta-analysis analyzed 23 clinical trials comprising 1,090 patients followed for 6 months and 441 patients followed for 1 yr postsurgery. The authors reported that perioperative epidural analgesia was able to decrease persistent postoperative pain in thoracotomies, abdominal surgeries, and breast surgeries. However, no data were reported on when or how long the epidural should be used to have a significant impact on persistent postoperative pain. Finally, when placed for abdominal surgery, epidural was not found capable to reduce the chronic use of opioids after such surgeries.[137]

**Peripheral Nerve Blocks.** Only a few studies with small numbers of patients, variable surgical procedures, and a variety of regional nerve blocks have been performed to evaluate their effectiveness in preventing persistent postoperative pain.[138] Although no definitive conclusion can currently be made, there is evidence that regional anesthesia for breast, knee, and hip surgery can reduce the incidence of persistent postoperative pain at 1 yr.[5,125,126] These promising results are tempered by a systematic review that reported no differences in the incidence of persistent postoperative pain at 1 yr postsurgery.[127] Whenever feasible, continuous peripheral nerve block seems to be adapted to limit persistent postoperative pain development. However, as reported for epidurals, nerve catheter use for knee or shoulder surgeries do not impact and do not decrease the risk of developing chronic opioid use after such surgeries.[139,140]

**Continuous Wound Infiltration or Continuous Surgical Site Analgesia.** Few randomized studies have evaluated continuous wound infiltration or continuous surgical site analgesia as alternatives to epidural analgesia to prevent persistent postoperative pain. A recent prospective randomized trial[99] compared continuous surgical site analgesia, epidural analgesia, and patient-controlled analgesic morphine in patients undergoing open nephrectomy. Continuous infiltration of 0.2% ropivacaine significantly reduced the severity of residual pain and optimized quality-of-life parameters 3 months after surgery. Persistent postoperative pain limitation was related to the decrease of wound hyperalgesia area during the first postoperative 72 h. After iliac crest grafting for orthopedic surgery, a continuous infusion of 0.2% ropivacaine compared to saline is reported as an effective method for persistent postoperative pain limitation after 3 months.[123] In contrast, a study comparing ropivacaine or placebo infiltration of the wound, the second and third intercostal spaces, and the humeral insertion of major pectoralis after breast cancer surgery reported no persistent postoperative pain prevention at 3, 6, and 12 months postoperatively.[128] Continuous wound infiltration impact on persistent postoperative pain is still debated and is probably mostly related to surgery and patient preoperative factors.

**Intravenous Lidocaine.** Very few studies have evaluated the impact of IV lidocaine on persistent postoperative pain. In 36 patients scheduled for breast surgery, lidocaine was given as an IV bolus of 1.5 mg/kg at the induction of anesthesia and then intraoperatively as an IV infusion at 1.5 mg $kg^{-1}$ $h^{-1}$ until 1 h after skin closure. Persistent postoperative pain assessment at 3 months showed that IV lidocaine was able to reduce the incidence from 47 to 12%, with less residual pain at movement and a lower area of hyperalgesia in the lidocaine group.[141] In a meta-analysis published in 2016 on only four clinical reports, it was reported that IV lidocaine administered for breast surgery did not change acute pain scores but significantly reduced analgesic consumption in the early days after surgery, and it slightly decreased the incidence of persistent postoperative pain (odds ratio, 0.332; 95% CI, 0.141 to 0.781; $P = 0.012$).[122]

### *NMDA Receptor Antagonists*

**Ketamine.** By blocking the activity of the NMDA receptors, ketamine is effective in reducing central pain sensitization produced by injury and/or opioid administration that may explain its beneficial effects in reducing acute postoperative pain.[142–144] Then IV ketamine is sometimes combined for 48 h with the opioid analgesic patient-controlled analgesia. However, its effectiveness on acute postoperative pain is still controversial when given this way.[145–147] Therefore, ketamine is often given as a solution through a separate infusion pump.

During the last decade, the results on the role of ketamine in preventing persistent postoperative pain are conflicting. One very early study showed strong reduction of the incidence of residual pain until the sixth postoperative month after laparotomies.[148] Similar results were reported in hip surgery.[149] Few other studies failed to report a positive impact of ketamine on persistent postoperative pain.[150]

Three recent systematic reviews and meta-analyses on the impact of ketamine on the development of persistent postoperative pain were published.[151–153] In a systematic review of the literature published in the Cochrane Database of Systematic Reviews, Chaparro *et al.*[152] reported interesting mixed results on the impact of perioperative administration of ketamine on the development of persistent postoperative pain. Only 14 studies reached the criteria of selection to enter this systematic review and meta-analysis looking at persistent postoperative pain at 3, 4, and 6 months after surgery. The patients were scheduled for abdominal, orthopedic, amputation, breast, and thoracic surgeries. Interestingly, at 3 months there was no impact of ketamine on persistent pain. Nevertheless, authors reported that they could show a significance difference in terms of persistent postoperative pain at 3 months when they analyzed the subgroup of patients who received ketamine for more than 24 h. Only one study looked at 4 months of persistent postoperative pain that was then not evaluated in their analysis.[150] Finally, when they evaluated the effect of perioperative ketamine on the risk of developing persistent postoperative pain at 6 months after surgery, they reported a beneficial impact of ketamine administration in diminishing the development of persistent

postoperative pain (odds ratio, 0.5; 95% CI, 0.33 to 0.76). Nevertheless, in this analysis at 6 months postsurgery, they were unable to show that giving ketamine for more than 24 h after surgery would have a higher impact on the 6 months of persistent postoperative pain than administering ketamine for less than 24 h.

More details on ketamine administration were provided in 2014 by another systematic review and meta-analysis on ketamine use for the prevention of persistent postoperative pain. McNicol *et al.*[151] screened 538 records; 43 articles were assessed for eligibility. Among these 43 articles, 17 were eligible for inclusion in the qualitative and quantitative analyses. Most of these studies were the same as those reported in the 2013 Chaparro *et al.*[152] meta-analysis cited above. Authors reported that the meta-analysis of the eligible studies evaluating IV and epidural administration of ketamine to prevent persistent postoperative pain did not show a significant reduction of persistent postoperative pain at 3 and 6 months. Nevertheless, when only studies with IV administration of ketamine were evaluated (excluding studies with epidural ketamine administration), authors concluded that IV ketamine prevents persistent postoperative pain at 3 and 6 months (3 months: odds ratio, 0.75; 95% CI, 0.6 to 0.93; and 6 months: odds ratio, 0.7; 95% CI, 0.5 to 0.98). This led them also to conclude that epidural administration of ketamine has no effect on persistent postoperative pain and, moreover, might have some direct neurotoxicity.

Finally, the most recent review on the impact of ketamine on persistent postoperative pain was published in 2015 by Klatt *et al.*[153] These authors included 10 articles from the literature in their comprehensive meta-analysis, for a total of 784 patients. Three articles (303 patients) showed a positive outcome concerning persistent postoperative pain. They analyzed the outcomes differently from the two above-cited reviews. Indeed, they analyzed pain criteria more precisely such as postoperative pain at rest or in motion after 1, 3, 6, or 12 months, defined as a value greater than or equal to 3 on a visual analog scale of 0 to 10, whereas previous meta-analysis evaluated only the presence or the absence of pain without precise scoring. Klatt *et al.*[153] then concluded that there is currently insufficient evidence to support a reduction in chronic pain or persistent postoperative pain due to perioperative administration of ketamine.

The difficulty of conducting such clinical studies on persistent postoperative pain leads to a very small number of clinical trials and a small number of patients, multiple biases, and a high level of difficulty in drawing meaningful conclusions. Thus, further studies on larger number of patients are needed.

**Nitrous Oxide.** Nitrous oxide is also an NMDA antagonist. It has been shown to be able to reduce acute opioid induced hyperalgesia after surgery in both rodents[154] and humans.[155] Nevertheless, no clinical trial prospectively assessed the effect of nitrous oxide in preventing persistent postoperative pain. A single retrospective analysis of data from a study designed for other purposes suggested a possible preventative effect of nitrous oxide on the development of persistent postoperative pain.[156]

**Dextromethorphan.** Dextromethorphan is known to block the activation of the NMDA receptors. A recent meta-analysis suggests that perioperative dextromethorphan reduces the postoperative opioid consumption at 24 to 48 h and pain scores at 1, 4 to 6, and 24 h.[157] This observation suggests that dextromethorphan could be part of the therapeutic arsenal for anesthesiologists to manage persistent postoperative pain. However, no clinical data support its beneficial effects in preventing postoperative pain.

### *Anticonvulsants*

**Gabapentin and Pregabalin.** Gabapentinoids produce an inhibitory modulation of neuronal excitability by blocking the α2–δ subunit of the presynaptic, voltage-dependent calcium channels, which are up-regulated in central sensitization processes. Their efficacy in the treatment of chronic pain of neuropathic origin is well recognized. In addition, their role in improving postoperative pain management by reducing opioid consumption and pain scores has been widely reported. Nevertheless, both gabapentin and pregabalin are responsible for strong side effects such as sedation, dizziness, and visual troubles.[152,158–161] For some authors, the balance between clinical advantages and side effects is sufficiently unclear to conclude on the use of gabapentinoids even for acute postoperative pain management.[162] Their role in preventing persistent postoperative pain is also still debated.

***Gabapentin.*** Most clinical trials failed to demonstrate any reduction in the incidence of persistent postoperative pain with gabapentin at 3 and 6 months after thoracotomy, cesarean section, cardiac and breast surgery, and amputation. The best results on persistent postoperative pain were observed with higher doses of gabapentin (1,200 to 1,800 mg orally) at the price of strong side effects as described above. Nevertheless, when these studies are pooled into the meta-analyses of Chaparro *et al.*[152] and Clarke *et al.*,[161] the authors were unable to show a strong impact of gabapentin on persistent postoperative pain at 3 months postsurgery. The most recent clinical trial published on this topic is not included in the meta-analyses cited above, but it also reported no difference in persistent postoperative pain in thoracic surgery at 3 and 6 months when gabapentin was given orally with an optimal regimen: a premedication of 1,200 mg orally and then every day at increasing doses ranging from 600 to 1,200 mg for 5 consecutive postoperative days.[163]

***Pregabalin.*** The same two meta-analyses by Chaparro *et al.*[152] and Clarke *et al.*[161] indicated that pregabalin significantly reduced the incidence of persistent postoperative pain after cardiac, spine,[164] thyroid, and knee surgery at 3 months (odds ratio, 0.70, 95% CI, 0.51 to 0.95, 5 studies[152]; and odds ratio, 0.09, 95% CI, 0.02 to 0.079[161]) but not at 6 months[165] and 12 months.[166] Most often, pregabalin 150 to 300 mg was initiated

before surgery and continued 75 to 150 mg twice daily for 2 to 14 days. However, significant heterogeneity and some biases in the reported trials might have exaggerated these results. In addition, the meta-analyses did not include three large unpublished trials that all yielded negative results (NCT00442546, NCT00468845, and NCT00551135). Three recent studies published in 2015 after the two meta-analyses cited above demonstrated no effect of pregabalin on persistent postoperative pain 3 months after total knee arthroplasty,[167] hip arthroplasty,[168] and thoracotomy[169] and also reported more side effects such as sedation and less patient satisfaction when pregabalin was given.[167] Last, the most recent meta-analysis done on pregabalin alone and not gabapentin suggested that pregabalin might be effective for the reduction of neuropathic persistent pain as Chaparro *et al.*[152] and Clarke *et al.*[161] previously suggested, but the number of studies was too limited to draw strong a conclusion on this outcome.[160] More studies are still needed.

### α2 Agonists

**Clonidine and Dexmedetomidine.** Clonidine, an α2-adrenergic receptor agonist with peripheral and central mechanism of action,[170,171] was proposed to treat acute or chronic pain despite some well reported hemodynamic side effects. Neuraxial administration (epidural or intrathecal) seems to lessen these side effects. Animal studies and clinical trials showed interesting results of IV or intrathecal clonidine administration on acute pain and hyperalgesia after surgery.[143,172–174] Nevertheless, to date, there are only three prospective studies that evaluated the effect of clonidine given perioperatively on the prevention of persistent postoperative pain with a small number of patients. One of these studies was on lower-limb amputation with a very poor design that was neither randomized nor properly blinded.[175] Among multiple outcomes on acute pain management in their study, De Kock *et al.*[96] also reported in 2006 results on the impact of clonidine on persistent postoperative pain. They showed that intrathecal clonidine 300 μg was better than intrathecal bupivacaine in reducing persistent postoperative pain occurrence at 6 months after colorectal surgery: no patient in the clonidine group developed persistent postoperative pain, whereas 6 of 20 patients in the control group developed persistent postoperative pain. A third study by the same group[97] reported that epidural administration of local anesthetic associated with opioid and systemic ketamine was better than IV clonidine and opioid and systemic ketamine in preventing persistent postoperative pain after laparotomy for colon surgery. Nevertheless, multiple questions were raised about this study,[176] and persistent postoperative pain was not the primary outcome of this study. In summary, it is difficult to conclude on the use of clonidine to prevent the development of persistent postoperative pain to date, considering the low number of both patients and studies. Larger studies are needed with a primary outcome defined as persistent postoperative pain reduction.

Only one study was reported on the effect of perioperative dexmedetomidine to reduce the risk of developing persistent postoperative pain.[177] This double-blinded study evaluated 84 patients scheduled for breast surgery and looked at persistent postoperative pain reduction as the primary outcome. Patients received IV dexmedetomidine infusion for 24 h *versus* placebo and showed persistent postoperative pain after breast surgery in 20% of patients in the dexmedetomidine group *versus* 54% in the placebo group. All qualitative aspects of persistent postoperative pain showed a better profile in the dexmedetomidine group. One single study in one single type of surgery and only 84 patients cannot allow to conclude on the use dexmedetomidine to prevent the development of persistent postoperative pain. Further future studies are needed here too.

### Other Clinical Considerations

Initially, we described how high doses of intraoperative opioids can induce postoperative hyperalgesia. Reduction in perioperative opioids by utilizing some of the described strategies for sparing opioids could be considered to limit the possible incidence of perioperative opioid on postoperative pain. Other possible interventions include less invasive surgical procedures that minimize nerve damage. Three examples of surgical options that will very likely change the long-term outcome of patients in terms of persistent postoperative pain[9] are preservation of intercostal brachial nerve in mastectomy, minimally invasive nerve-sparing techniques for thoracotomies, and more precise dissection of the inguinal area to avoid nerve damage. During the last decade, many reviews have been well written on the subject.[21]

## Conclusions and Future Directions

Persistent postoperative pain is a complex biopsychosocial phenomenon that, once initiated, is difficult to control and often difficult to treat. Its incidence varies across individuals and procedures.[8,178–180] It remains a critical factor that affects the quality of life of our patients. Animal studies using incisional pain model suggest that the development of persistent postoperative pain should be considered both as a pain sensitization process and also as a failure to adjust to the exaggerated activation of pain facilitatory systems due to the surgery.

Blocking or limiting persistent pain sensitization postsurgery is clearly important in the prevention of persistent postoperative pain. For anesthesiologists, some available drug candidates should be combined pre-, intra-, and postoperatively to limit nociceptive input–induced pain sensitization as much as possible. Accordingly, further well-designed controlled clinical studies are needed to firmly evaluate the beneficial effects of the different available strategies to support anesthesiologists in preventing persistent postoperative pain.

It is important that we develop and engage new therapies (multimodal pharmacologic approaches) to prevent or reduce the risk of persistent postoperative pain. For this purpose, science research requires translation into clinical studies. For instance, but not limited, future options for treatment might include the use of anti-nerve growth factor or treatments

aimed at restoring the function of endogenous analgesia such as Nav1.7 antagonist. Epigenetics is also emerging as a promising field of research. As previously proposed, the epigenetic potential of widely used drugs in the perioperative settings needs to be investigated in the near future.[74]

## Acknowledgments

The authors thank Patrick Carroll, Ph.D., National Institute of Health and Medical Research, U1051, Montpellier, France, for his comments and his assistance in editing the manuscript.

## Research Support

Supported by the National Institute of Health and Medical Research, Montpellier, France (to Dr. Rivat and Dr. Capdevila), the Department of Anesthesiology and Critical Care Medicine, Lapeyronie University Hospital, Montpellier, France (to Dr. Capdevila), and the Department of Anesthesiology and Pain Medicine, Maisonneuve-Rosemont Hospital, University of Montreal, Montreal, Quebec, Canada (to Dr. Richebé).

## Competing Interests

Dr. Richebé received an honorarium from Medtronic/Covidien (Kirkland, Canada) as a consultant and funds from Medasense Ltd. (Ramat Gan, Israel) as a consultant and member of the scientific advisory board. Dr. Richebé also received funds for Independent Investigator Initiated Trials in the last 3 yr with Air Liquide USA (Newark, Delaware), Ferring (North York, Canada), and Medasense Ltd.

## Correspondence

Address correspondence to Dr. Rivat: Université de Montpellier, Institut des Neurosciences de Montpellier INSERM U1051, Hôpital Saint Eloi, 80, rue Augustin Fliche, 34091 Montpellier-Cedex 5, France. cyril.rivat@umontpellier.fr. 

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