

Transition from acute to chronic postsurgical pain: risk factors and protective factors

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Most patients who undergo surgery recover uneventfully and resume their normal daily activities within weeks. Nevertheless, chronic postsurgical pain develops in an alarming proportion of patients. The prevailing approach of focusing on established chronic pain implicitly assumes that information generated during the acute injury phase is not important to the subsequent development of chronic pain. However, a rarely appreciated fact is that every chronic pain was once acute. Here, we argue that a focus on the transition from acute to chronic pain may reveal important cues that will help us to predict who will go on to develop chronic pain and who will not. Unlike other injuries, surgery presents a unique set of circumstances in which the precise timing of the physical insult and ensuing pain are known in advance. This provides an opportunity, before surgery, to identify the risk factors and protective factors that predict the course of recovery. In this paper, the epidemiology of chronic postsurgical pain is reviewed. The surgical, psychosocial, socio–environmental and patient-related factors that appear to confer a greater risk of developing chronic postsurgical pain are described. The genetics of chronic postsurgical pain are discussed with emphasis on known polymorphisms in human genes associated with chronic pain, genetic studies of rodent models of pain involving surgical approaches, the importance of developing accurate human chronic postsurgical pain phenotypes and the expected gains for chronic postsurgical pain medicine in the post-genomic era. Evidence is then reviewed for a preventive multimodal analgesic approach to surgery. While there is some evidence that chronic postsurgical pain can be minimized or prevented by an analgesic approach involving aggressive perioperative multimodal treatment, other studies fail to show this benefit. The transition of acute postoperative pain to chronic postsurgical pain is a complex and poorly understood developmental process, involving biological, psychological and social–environmental factors.

KEYWORDS: animal model • chronic postsurgical pain • neuropathic pain • pain genetics • pain phenomics • pre-emptive analgesia • preventive analgesia • psychosocial risk factor

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1]. There is, however, no one accepted definition of chronic postsurgical pain and it is debatable whether, at the present time, a single definition would be useful [2]. Most attempts at defining chronic postsurgical pain, whether general [3] or specific to a surgical procedure [4,5], are descriptive in nature and offer a time frame for chronicity beginning 2 or 3 months after surgery. Macrae and Davies propose the following four-point definition of chronic postsurgical pain: “the pain developed after a surgical procedure; the pain is of at least

2 months duration; other causes for the pain have been excluded; the possibility that the pain is continuing from a pre-existing problem should be explored and exclusion attempted” [2].

Most patients who undergo surgery recover uneventfully and resume their normal daily activities within weeks. However, chronic postsurgical pain develops in an alarming proportion of patients. The magnitude of the problem is evidenced by recent epidemiological data documented later. A fact that is rarely appreciated by pain clinicians and researchers is that every chronic postinjury or postsurgical pain was once acute; the development of chronic postsurgical pain involves a transitional process. The traditional, dominant focus on studying established

chronic pain misses important cues that may help us to predict who will go on to develop chronic postsurgical pain and who will recover uneventfully. Emphasis on identifying the processes that underlie the transition to chronicity has been a neglected topic of investigation. The aim of this review is to critically examine the factors that are associated with the development of chronic postsurgical pain. We first review available data on the epidemiology and course of chronic postsurgical pain following various surgical procedures. We then describe the surgical, psychosocial, social–environmental and patient-related factors that appear to confer a greater risk of developing chronic postsurgical pain. We also discuss the genetics of chronic postsurgical pain, with an emphasis on known polymorphisms in human genes associated with chronic pain in general, pain genetic studies of rodent models involving surgical approaches, the importance of developing accurate human pain phenotypes and the expected gains for chronic postsurgical pain medicine in the postgenomic era. Finally we review the evidence suggesting that a preventive analgesic approach can reduce the incidence and intensity of chronic postsurgical pain. We conclude with key issues, an expert commentary and a 5-year view into the future.

Epidemiology of chronic postsurgical pain

TABLE 1 shows the incidence of chronic postsurgical pain following a variety of surgical procedures, including limb amputation, thoracotomy, mastectomy, hernia repair, open cholecystectomy, cesarean section, hip replacement and median sternotomy for coronary artery bypass graft surgery. This table illustrates the growing awareness of chronic postsurgical pain [6–9]. For example, a prospective study of approximately 5000 patients estimated the incidence of acute neuropathic pain in the days after surgery to be between 1 and 3% [10]. A 1-year follow-up showed that 56% of the patients with acute neuropathic pain continued to have pain [10]. Other reports suggest the incidence of acute postsurgical neuropathic pain is considerably higher [11] and, given the 56% rate of conversion to chronicity [11], support the view that up to 10% of patients report severe, intractable chronic postsurgical pain 1 year after surgery. These statistics are staggering, especially when one considers the total number of patients worldwide who undergo surgery each year. It is not at all surprising, then, to see that almost 25% of more than 5000 patients referred to chronic pain treatment centers have chronic postsurgical pain [12].

We know next to nothing about pain beyond the 1-year mark. Most studies followed patients for approximately 1 year after surgery. The data show the 1-year incidence to be highly variable and surgery specific, ranging from a low of approximately 10–15% following modified radical mastectomy [13] to a high of 61–70% for thoracotomy [14] and amputation [15]. Follow-up beyond the 1-year mark is not common but there are two studies of patients followed for up to 5 or 6 years after hernia repair and two studies of lower limb amputees followed for 2 years. The longer term hernia repair follow-up data indicate that pain persists in 8.1–19% of patients for up to 6 years, with severe or very severe pain occurring in 1.8%. A total of 2 years after amputation approximately

60% of amputees report phantom limb pain (PLP) and 21–57% report stump (residual limb) pain [16,17]. These studies indicate that even the lowest incidences are unacceptably high.

Some of the variability in these estimates can be accounted for by the criterion used to classify patients as having chronic pain; the more stringent the criterion, the lower the estimate. For example, studies that measure the intensity of pain or the impact of pain on daily activities show that the incidence of chronic postsurgical pain is lower when the cut-off for severity and impact of pain is high [14–16,18–21]. Other reasons for the variability in estimates for a given surgical procedure include lack of precision in defining/diagnosing chronic postsurgical pain, sampling method, source of patients, their genetic background and whether the classification of the pain as chronic was by self-report. Despite this variability, even the most conservative estimates are a cause for concern.

Factors associated with chronic postsurgical pain

Surgical factors associated with chronic postsurgical pain

The following surgical factors are associated with an increased likelihood of developing chronic postsurgical pain: increased duration of surgery [22,23], low (vs high) volume surgical unit [13], open (vs laparoscopic) approach [24], pericostal (vs intracostal) stitches [25], conventional hernia repair [24] and intraoperative nerve damage [10,24]. Whether these factors are causally related to the development of chronic pain is not known. However, these factors appear to have in common greater surgical trauma and, in particular, they point to intraoperative nerve injury as a likely causal mechanism. Nerve damage produces acute and lasting changes in the injured nerves, and even in their intact neighboring nerves, pain pathways in the CNS, and motor and sympathetic outputs (reviewed by Devor and Seltzer [26]). These changes are probably the main culprit in producing both acute and chronic neuropathic pain.

More than 30 years of basic science research has shown that nerve injury produces neuropathic conditions and behaviors in rodents that resemble symptoms of chronic neuropathic pain in humans (for reviews see [27,28]). In fact, the most commonly used animal models of neuropathic pain involve intentional damage to peripheral nerves [29–32] or spinal nerves [33], by total nerve section [29,32,33], or partial nerve ligation [31] or constriction [30]. Using these models enabled investigators to identify a number of intraoperative methodological factors. The type of knife that was used when cutting tissues and nerves affected neuropathic pain-related behavior in a rodent model of limb amputation pains and anesthesia dolorosa. Electrocautery was associated with significantly more chronic pain than was use of a laser [34]. In a model of brachial plexus avulsion following hindpaw deafferentation, it was found that using ketamine and xylazine for general anesthesia significantly reduced the incidence of neuropathic pain when compared with anesthesia using a barbiturate, suggesting that improvements in the type of general anesthetic used during surgery may reduce pain chronicity [35].

One of the triggers of pain chronicity is thought to be the amount of injury discharge produced intraoperatively and its impact on the CNS. When a peripheral nerve is transected or otherwise injured,

Table 1. Incidence of chronic postsurgical pain following various surgical procedures.

Study	Surgical procedure	Patients with data in study (n)	Follow-up time (postoperation)	Incidence of chronic postsurgical pain (%)	Ref.
Tasmuth <i>et al.</i> (1997)	MRM or BCT with axillary clearance	93 MRM = 53 BCT = 40	1 year	Breast region: MRM = 17 BCT = 33 Ipsilateral arm: MRM = 13 BCT = 23	[96]
Aasvang <i>et al.</i> (2006)	Hernia repair	694	1 year	Inguinal pain = 56.6 Ejaculation pain = 18.3 Pain in: Testes = 39.7 Shaft = 5.4 Glans = 4.5 Thigh = 11.6	[202]
Grant <i>et al.</i> (2004)	Hernia repair		5 years	Groin pain = 19 Severe or very severe groin pain = 1.8 Testicular pain = 16.1	[21]
Bay-Nielsen <i>et al.</i> (2001)	Hernia repair	1166	1 year	Pain in groin area = 28.7 Pain interfering with work or leisure = 11	[20]
Aasvang <i>et al.</i> (2006)			6.5 years	Chronic inguinal pain = 8.1	[203]
Katz <i>et al.</i> (1996)	Thoracotomy	23	1.5 years	Dull, aching or burning pain on a daily to weekly basis = 52 Mean pain intensity: 3.3/10	[94]
Pertunnen <i>et al.</i> (1999)	Thoracotomy	67	1 year	Postthoracotomy pain = 61 Severe pain = 3–5	[14]
Gotoda <i>et al.</i> (2001)	Thoracotomy	91	1 year	Post-thoracotomy pain: Pain free = 59 Slight pain = 39 Moderate pain = 2 Severe pain = 0	[19]
Nikolajsen <i>et al.</i> (2004)	Caesarean section	220	~1 year	Abdominal scar pain = 12.3	[204]
Nikolajsen <i>et al.</i> (1997)	Amputation	60	1 year	Phantom limb pain = ~70	[15]
Richardson <i>et al.</i> (2006)	Amputation	52	6 months	Phantom limb pain = 78.8 Stump pain = 51.2	[205]
Jensen <i>et al.</i> (1985)	Amputation	58	2 years	Phantom limb pain = 59 Stump pain = 21	[17]
Hanley <i>et al.</i> (2007)	Amputation	57	2 years	Phantom limb pain intensity > 0/10 = 62 Phantom limb pain intensity > 3/10 = 30 Stump pain intensity > 0/10 = 57 Stump pain intensity > 3/10 = 27	[89]
Borly <i>et al.</i> (1999)	Open cholecystectomy	80	1 year	Pain = 26	[53]
Meyerson <i>et al.</i> (2001)	Sternotomy for cardiac surgery	318	1 year	Post-sternotomy pain = 28 With pain intensity \geq 30/100 = 13	[18]
Nikolajsen <i>et al.</i> (2006)	Hip replacement	1048	12–18-month prevalence	Chronic hip pain = 28.1 Pain limited activities to a moderate, severe or very severe degree = 12.1	[166]

BCT: Breast-conserving surgery; MRM: Modified radical mastectomy.

it emits a long-lasting, high-frequency burst of activity [36,37]. This injury discharge involves a train of impulses produced by freshly injured afferent nerve fibers (ruptured myelinated and unmyelinated axons) that uses glutamatergic neurotransmission via NMDA receptors to sensitize nociceptive pathways in the CNS. Injury discharge is under tonic endogenous inhibition by inhibitory interneurons in the spinal cord that use amino acids, such as GABA and glycine [38]. The massive glutamatergic activation of postsynaptic NMDA receptors on interneurons in the spinal dorsal horn, many of which are inhibitory [39], is believed to be excitotoxic, leading to their destruction and to disinhibition of pain pathways [40–42]. Thus, one very useful preventive measure that can be taken when it comes to humans undergoing surgery is to avoid intraoperative nerve damage. Obviously, this is not possible for certain surgeries, such as limb amputation, that involve ligation and section of major nerve trunks. However, the practice of intentionally transecting nerves for surgical convenience should be avoided [24] and doing so will, without doubt, contribute to a lower incidence of neuropathic pain [6,43].

Note, however, that many operations do not result in transecting nerve trunks, but in stretching or crushing nerves during retraction of tissues when accessing deeper structures, or in cutting skin, fascia, muscles, joints, bony structures and viscera, all of which are innervated by sensory fibers. Thus, injuring such afferents by stretching the nerve trunk or the tissue it innervates, cauterizing or trapping it in a suture or clips, or cutting the tissue may be a trigger for increased acute postsurgical pain and possibly the transition to pain chronicity. In fact, there is a rodent model that mimics this type of injury by simply cutting skin and underlying muscle without damaging a nerve trunk. The incision proposed in the original model was cutting the thigh skin and underlying biceps femoris muscle [44]. This injury produced small-to medium-sized, pyknotic and hyperchromatic neurons ('dark neurons') in the upper spinal dorsal horn laminae that process nociceptive input. It has been proposed that these changes are produced by an excitotoxic insult involving NMDA receptor activation subsequent to injury discharge, and that at least some of these neurons are inhibitory interneurons whose functional impairment or death contributes to a central state of hyperexcitability that underlies neuropathic hyperalgesia and allodynia [44]. A few years later, this model was slightly modified by making the incision on the plantar surface of the hindpaw of the rodent, cutting through skin and muscle, thereby producing heat and mechanical allodynia and hyperalgesia, and guarding behavior that, in the rat, lasted 6 days [45]. Subsequent work showed that the heat allodynia and spontaneous firing of impulses in C-fibers, innervating the skin adjacent to the incision, depended on Vanilloid 1 transient receptor potential (Trpv1) receptors, and the allodynia and firing of C-fibers were much reduced in *Trpv1* gene knockout mice [46]. Treating rats that had undergone the plantar postincision pain model with the Trpv1 antagonist AMG0347 decreased capsaicin-induced heat and mechanical hyperalgesia [47]. This model is sensitive to opiate treatments, since a small dose of morphine affected guarding behavior and responses to noxious abnormal heat stimuli [48]. NGF and TNF- α play a role in mediating the

sensory abnormalities in this model, as they do in other models of neuropathic pain following nerve injury [49,50]. However, neither gender nor strain (i.e., genetic variation) effects were noted across mice of the DBA2/J, C57BL/6J and 129X1/SvJ strains [51]. Since the latter two are routine strain platforms for the study of gene knockout studies, this confirms that the plantar incision model can be used to detect gene effects on the sensory abnormalities that characterize it.

Another variant of the skin and muscle incision model of Nachemson and Bennett [44] was adapted for laparotomy, by having the incision performed in rats at a subcostal level accessing the peritoneal cavity [52]. The surgical procedure produced decreased ambulation and rearing by approximately 50% 24 h after surgery, which was reversed by morphine (but not the rearing) and ketorolac. There were synergistic effects when the two analgesics were coadministered. This model mimics the behavioral aspects of postoperative pain seen clinically, including the reported analgesic efficacy and occurrence of side effects found with these agents in humans [52].

Psychosocial factors & chronic postsurgical pain

Only recently have researchers begun to examine psychosocial risk factors associated with the development of chronic postsurgical pain. Several psychosocial predictors of chronic postsurgical pain [23,53,54] or chronic postsurgical pain disability [16,55] have been identified, including increased preoperative state anxiety [56], an introverted personality [53], less catastrophizing, social support and solicitous responding in the week after amputation [16,55], higher concurrent emotional numbing scores at 6 and 12 months [57], fear of surgery [23], and 'psychic vulnerability' [54], a construct similar to neuroticism [9]. Solicitous responding includes behaviors on the part of significant others that unwittingly positively and/or negatively reinforce the patient's pain behaviors thereby increasing their frequency of occurrence. For example, in response to a complaint of pain or a grimace from the patient when performing a household chore, an empathic spouse may tell the patient to rest while she performs the task herself. Such solicitous behaviors may, in some instances, have the unintended consequence of increasing the frequency of pain behaviors and thus contributing to pain-related disability.

Catastrophizing

Pain catastrophizing is characterized by unrealistic beliefs that the current situation will lead to the worst possible pain outcome [58], negative thoughts about the future and self [59] and "an exaggerated negative 'mental set' brought to bear during actual or anticipated pain experience" [60]. Pain catastrophizing is a multidimensional construct comprising elements of rumination, magnification and helplessness [60–62]. One of the few consistent findings in the pain literature is that chronic pain patients who do not catastrophize fare better than patients who do catastrophize [63].

Jensen *et al.* [55] and Hanley *et al.* [16] evaluated a biopsychosocial model predicting pain interference (disability) and depression in a 2-year prospective study of 70 patients initially assessed 1 month after lower limb amputation. Patients completed a measure of PLP intensity and the following psychosocial measures 1 month,

6 months [55], 1 year and 2 years [16] after amputation: pain cognitions (catastrophizing, perceived control over pain), pain coping, social support, social environment (solicitous responding from a significant other), pain interference and depressive symptoms. Regression analyses showed that 1-month pain and psychosocial measures accounted for a total of 46% of the variance in pain interference change scores at the 2-year follow-up. Psychosocial measures accounted for 27% of the variance, with catastrophizing, social support and solicitous responses each accounting for a unique and statistically significant portion of the variance. Greater social support and less spousal solicitousness (indicating, for example, a lesser tendency for spouses to attend to complaints of pain and to take over the pain patient's jobs and duties) and, counterintuitively, more frequent catastrophizing at 1 month were associated with improvements (greater decreases) in pain interference scores 2 years later. In addition, 1-month pain and psychosocial measures accounted for a total of 36% of the variance in change in depressive symptoms at the 2-year follow-up, with only catastrophizing contributing a unique and statistically significant portion of the variance.

More frequent catastrophizing predicting better outcome appears to be a counterintuitive finding, and may be, in part, accounted for by the use-change scores that complicate interpretation. The authors note that those patients who catastrophized most at the initial assessment likely had more room for improvement in pain interference and depressive symptoms at the 2-year follow-up, suggesting that the findings may be an artifact of using difference scores and from a regression to the mean. The authors offered an alternative interpretation, suggesting that there may be something beneficial about pain catastrophizing early after amputation, either because it mobilizes social support resources that ultimately assist in recovery and adjustment or because it is associated with an acute, adaptive grief reaction that contributes to earlier long-term resolution of issues concerning limb loss. Alternatively, catastrophizers may seek and receive medical treatments early on that have a lasting effect on impulse generators in the amputated nerves and/or the CNS.

In a more recent prospective, longitudinal study, 55 patients scheduled to undergo total knee arthroplasty were assessed before and at several time points up to 2 years after surgery [64]. In contrast to McGill Pain Questionnaire (MPQ) pain scores, which decreased over time, catastrophizing scores remained relatively constant over the 2-year follow-up period. Regression analyses showed that preoperative catastrophizing of a ruminative nature significantly predicted MPQ pain ratings 2 years after surgery. It remains to be seen whether the relationship between preoperative catastrophizing and chronic postsurgical pain after total knee arthroplasty is causal or associative.

Social support & social–environmental factors

The relevance to chronic postsurgical pain of social support in general, and solicitous responding in particular, has been established in a 2-year prospective study of amputees with PLP [16,55]. The relationship between solicitous responding from significant others and the patients' chronic pain intensity and behaviors is

explained by well established operant conditioning principles. The operant model proposes that in offering pain contingent help (e.g., taking over household jobs) in response to pain behaviors (e.g., guarding, limping) and verbal expressions of pain, well-intentioned spouses unwittingly negatively reinforce the patient's pain behaviors, leading to an increase in their frequency of occurrence [65,66]. As noted previously, greater social support and less spousal solicitousness 1 month after amputation were associated with improvement in pain interference scores 2 years later.

Chronic postsurgical pain & post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) typically develops after exposure to an event or situation that is perceived to be threatening to the physical or emotional integrity of an individual. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision) diagnostic criteria [67] for PTSD cover three symptom clusters, including re-experiencing the traumatic event (e.g., nightmares and 'flashbacks'), emotional numbing (e.g., feeling detached from others), avoidance of thoughts, feelings and activities associated with the trauma and increased arousal (e.g., insomnia, exaggerated startle reflex and hypervigilance). Recent data show that chronic pain and PTSD are highly comorbid [68,69].

Salomons *et al.* presented two case reports of patients who developed PTSD following an episode of awareness under anesthesia [70]. For both patients, post-traumatic sequelae persisted for years and included pain symptoms that resembled, in quality and location, the very pain experienced during surgery. In addition to the similarity to the original pain, these pain symptoms were triggered by stimuli associated with the traumatic situation, suggesting that they were flashbacks to the episode of awareness under anesthesia. Both patients participated in individual, trauma focused, cognitive–behavioral therapy with successful resolution of the PTSD.

Katz *et al.* evaluated the relationship between the post-traumatic stress symptom (PTSS) emotional numbing and chronic postsurgical pain disability 6 and 12 months after lateral thoracotomy using a prospective, longitudinal design [57]. A total of 54 patients who were scheduled to undergo posterolateral thoracotomy for intrathoracic malignancies were recruited 1 week before surgery and completed validated questionnaires assessing pain disability and PTSS. Pain intensity and total morphine consumption were recorded 24 and 48 h after surgery; 6 and 12 months after surgery patients were telephoned to determine chronic postsurgical pain incidence, pain disability and PTSS. The incidence of chronic post-thoracotomy pain was 68.1 and 61.1% at the 6- and 12-month follow-ups, respectively. Multiple regression analyses showed that neither preoperative factors nor acute movement-evoked post-operative pain predicted 6- or 12-month pain disability. However, concurrent pain intensity and emotional numbing, but not avoidance symptoms, made unique, significant contributions to the explanation of pain disability at each follow-up (total $R^2 = 76.3$ and 63.9% at 6 and 12 months, respectively). Over time, the relative contribution of pain intensity decreased, while that of emotional numbing increased, indicating a progressive decoupling of pain

intensity and disability and a concomitant strengthening of the link between emotional numbing and disability. This suggested that pain may serve as a traumatic stressor that causes increased emotional numbing. The source of the emotional numbing is not known; it may arise from living with pain, which serves as a reminder of the cancer or living with a diagnosis of cancer, as well as the threat of and/or a recurrence of cancer. It is also possible that the emotional numbing is, in part, due to a previous unrelated traumatic event. Further research is needed to determine the role (if any) of the endogenous opioid system in mediating this effect. It is interesting to add in this context that there is a growing body of literature indicating that living with chronic pain is associated with structural changes (usually thinning) of the cortex in parts of the brain typically associated with aversive-affective processing of pain in the several chronic pain syndromes [71–75].

Kleiman *et al.* provided preliminary evidence for a construct termed sensitivity to pain traumatization (SPT), which describes the anxiety-related psychological and emotional reactions, as well as behavioral responses to pain that resemble symptoms of PTSD [76]. They evaluated the relationships among commonly used pain-related measures of anxiety and fear in 372 patients approximately 1 week prior to major surgery. Exploratory factor analysis (unrotated) of the combined scale items ($n = 79$) supported a two-factor solution accounting for 30 and 9.9% of the variance, respectively, and consisting of 75 items. Since the first factor included all but one item in the second factor, a one-factor solution better approximated the simple structure. A rotated (Varimax) solution suggested the existence of 11 small independent factors (each accounting for between 2 and 11% of the variance) comprising the same 74 items as in factor one of the unrotated solution, and accounting for 57.6% of the shared variance. The pattern of findings suggested that several lower order factors loaded on a single higher order factor, which they called SPT. Evidence for an overlap between SPT and PTSD symptoms involved clusters of lower order SPT factors describing intrusive thoughts, behavioral avoidance and hyperarousal. Importantly, SPT showed a strong and significantly positive correlation ($r = 0.52$) with the total score on the PTSD Checklist – Civilian Version suggesting good preliminary construct validity for SPT.

Taken together, the results of these studies [57,70,76] indicate that PTSSs are associated with concurrent [57,76] and subsequent [57,70] pain and pain disability, months to years later, but the nature of the mechanisms underlying these relationships remain to be determined. One possible reason for the high comorbidity of PTSD and chronic pain may be the substantial symptom overlap common to both disorders, including: anxiety and hyperarousal, attentional biases, avoidant behaviors, emotional lability, and elevated somatic focus [68]. The overlap in symptoms suggests the two disorders may be mutually maintaining [68,77]. The idea of mutual maintenance may be linked to a common or shared underlying psychological vulnerability that may depend on shared genetic determinants and which places at-risk individuals at greater risk of developing one or both disorders. Anxiety sensitivity has been identified as one of the trait vulnerability factors that predispose individuals to the development of chronic pain, PTSD or both [68].

The intractability of the two disorders is not surprising when viewed in the context of mutual maintenance and shared vulnerability models. This underscores the importance of screening for both disorders when either one is present. This may be especially relevant in patients scheduled for major surgery given that diagnosis and surgery are highly stressful events and that many individuals scheduled for surgery also have chronic pain.

From a treatment perspective, there is very little published on comorbid PTSD and chronic pain [78] and nothing published on patients scheduled for surgery. There is some evidence that a cognitive-behavioral perspective that addresses both disorders is essential; otherwise, treatment of one (and not the other) would be expected to lead to partial recovery or, if complete recovery occurred in one domain, recovery might be transient [68,70,78]. The decoupling of pain and PTSD symptoms with time would argue for the need of an early initiation of treatment. However, until we know more about the source and nature of the traumatic stressors that patients experienced, it may be premature to make treatment recommendations.

Patient-related factors associated with chronic postsurgical pain

One of the most consistent patient-related factors found to be associated with the development of acute and chronic postsurgical pain is concurrent or past pain [6,9,79,80]. This appears to be true across surgery types and regardless of time frame. The presence of preoperative pain, or its intensity or duration, is a risk factor for the development of severe early acute postoperative pain [81], acute pain days [13,17,82–84] and weeks [85] after surgery, as well as long-term postsurgical pain [17,24,57,64,82,85–90]. Not only does preoperative pain predict later pain, severity of acute postoperative pain in the days and weeks after surgery predicts pain after discharge [85,91] and is also a risk factor for the development of chronic postsurgical pain [10,89,92–100].

No other patient factor is as consistently related to the development of future pain problems as is pain itself. Female gender [81,85] and younger age [81,85,98] predict chronic postsurgical pain, but not with the consistency or magnitude with which pain predicts pain. What must be determined, however, is the aspect(s) of pain that is predictive. There are several possibilities for why pain predicts pain, including those that propose a causal or associative role. The following factors are not mutually exclusive:

- Intraoperative nerve damage and the injury discharge that it causes [36–38];
- Sensitization of nociceptors in the surgical field [93];
- Early postoperative ectopic activity in the regenerating sprouts of injured primary afferents and in somata of these fibers in dorsal root ganglia associated with the injured nerves [101], and even in somata of intact neurons in dorsal root ganglia neighboring those associated with injured nerves [102];
- Collateral sprouting from intact nociceptive A δ afferents that neighbor the field innervated by injured afferents [94,103];
- Central sensitization induced by the surgery and maintained by peripheral input [40,104–106];

- Structural changes in the CNS induced by perioperative nociceptive activity (e.g., disappearance of antinociceptive inhibitory interneurons in the spinal dorsal horn [41,42] centralization of pain and somatosensory pain ‘memories’ [105,107,108]);
- Heretofore unidentified pain genes that confer increased risk of developing intense acute pain and chronic postsurgical pain [109–114];
- Consistent response bias over time. Some individuals have a tendency to report more intense pain than other individuals [79]. Thus, they would report intense pain immediately after surgery as well as in the long term. Excluding this possibility is important for establishing other plausible mechanisms for the pain (e.g., see [94]);
- Psychological and emotional factors, including emotional numbing [57] and catastrophizing [16,55,64];
- Social from environmental factors, such as solicitous responding from significant others [16,55] and social support [16];
- Publication bias in which findings of a significant relationship between pain before and after surgery are published whereas negative findings do not make it into print.

Genetics of chronic postsurgical pain

The genetics of pain is a very young research field (for recent reviews see [112,113]). Therefore, it should come as no surprise that, as of yet, there are no published reports about genes predisposing humans for the transition of acute pain after surgery to chronic postsurgical pain. There are only a few reports that have identified polymorphisms in human genes associated with chronic pain. These include polymorphisms in the following genes: *5-HTTLPR* (the gene encoding the serotonin transporter) that were found to associate significantly with levels of migraine [115], burning mouth syndrome [116], irritable bowel syndrome [117] and fibromyalgia [118]; *IL1B* (encoding IL-1 β) plays a role in burning mouth syndrome [116]; *IL1RN* (encoding IL-1 receptor antagonist) and *MC1R* (encoding the melanocortin-1 receptor) in vulvodinia [119]; *IL23R* (which encodes a subunit of the receptor for IL-23) in Crohn’s disease [120]; *GCHI* (encoding GTP cyclohydrolase, an enzyme catalyzing tetrahydrobiopterin, BH₄, an essential cofactor for catecholamine, serotonin and nitric oxide production) has been implicated in persistent radiculopathic pain following surgical discectomy (note that the sought association in this study was not with pain postsurgery but with surgical alleviation of an existing chronic lumbar root pain that was caused by disk herniation) [121]; *COMT* (encoding catechol-*O*-methyl transferase, the enzyme that inactivates dopamine, epinephrine and norepinephrine in the nervous system) has been implicated in a number of chronic pain entities (for review see [122]); and polymorphisms in *CACNA1*, *ATPIA2*, *MTHFR*, *SCN1A* and the female hormone genes *ESR1*, *ESR2* and *FSHR* have been implicated in migraines (for review see [123]). Note, however, that in many of these studies it has not been established whether the identified genetic determinants were associated with chronic pain

indirectly, by producing a disease that carries a morbidity for chronic pain, or directly, by producing and maintaining chronic pain once having the disease.

Pain genetic studies that are relevant to chronic postsurgical pain in rodent models have yielded the following results. Note that these models were not explicitly developed to model chronic postsurgical pain *per se*, yet used surgical approaches to injure peripheral nerves, spinal nerves, dorsal roots and the spinal cord [26–33,124]. Some of these models were used to determine the level of heritability for spontaneous and stimulus-induced neuropathic pain [114] in evaluating genetic differences across lines and strains of mice and rats in traits relevant to chronic postsurgical pain in humans [110,111,125–130], and the effect of genetic and environmental interactions on chronic postsurgical pain-related behaviors in these models [131–133]. These models were also used to map chromosomal regions (termed quantitative trait loci) that harbor chronic postsurgical pain-related genes [114,125,131,134,135]. These intervals were mapped using sets of recombinant inbred lines that were produced by repeatedly breeding two inbred parental lines [125], or by genotyping F2 offspring of inbred lines that contrast on the chronic postsurgical pain strain under study [134]. Using gene-expression and proteomic methods, hundreds of genes and proteins were identified in dorsal root ganglia and spinal cord (but none in supraspinal structures as of yet) of mice and rats in chronic postsurgical pain-related models [136–143]. Furthermore, manipulations of individual genes by overexpression or deletion (in transgenic ‘knockout’ experiments), or by shutting off expression using siRNA or antisense oligodeoxynucleotide injections, have identified over 240 rodent genes that have some demonstrated role in various acute and chronic pain models, some of which are relevant to chronic postsurgical pain. The information about these genes and the models in which they were studied is accessible on the internet [301].

Phenomics of chronic postsurgical pain

A gene for chronic postsurgical pain is identified when evidence is presented of a statistically significant ‘association’ between a pain trait characterizing chronic postsurgical pain and a genetic marker, usually a single nucleotide polymorphism in or near these genes. Thus, discovering such genes critically depends on the pain traits collected from participants in a given cohort. There is currently no consensus over what these pain traits should be; moreover, ‘pain phenomics’, the research field that constructs questionnaires and other tools to collect clinically-relevant phenotypic pain data for genetic studies, has not been born as of yet. Consequently, phenomic questionnaires for chronic pain are currently unavailable but critically important to the identification of genes for chronic postsurgical pain. Chronic postsurgical pain, like other chronic pain syndromes, is multifaceted, characterized by multiple sensory–discriminative, affective–emotive and cognitive–evaluative variables. In order to identify genes for these dimensions/aspects and solve clinical problems of chronic postsurgical pain by addressing the neural structures and networks that bring them about, one should faithfully characterize each patient in as much detail as is practical. It is not enough to collect from the

participants a categorical answer as to whether or not he/she has chronic postsurgical pain, and it is also not enough to limit the description of chronic postsurgical pain to the intensity of pain on a 0–10 visual analog scale. This is because there may very well be different genes controlling the interindividual variability in pain intensity of a typical pain episode, different genes for the frequency of such episodes, other genes for the amount of suffering the pain causes, additional genes for the type of the pain (e.g., ‘burning’ vs ‘electrical shock-like’), yet different ones for the spread of pain beyond the surgical field where nerves were injured and so on. Therefore, if we are to provide a comprehensive solution to chronic postsurgical pain based on genetics, we must develop tools and questionnaires to collect from every participant in a genetic study a broad array of phenotypes (i.e., quantifiable pain traits).

Expected gains for chronic postsurgical pain medicine in the postgenomic era

It is expected that a replicated genome-wide association study of chronic postsurgical pain, if powered statistically to detect genetic variations of small effects, followed by gene validation experiments, will discover most genetic variations that affect the transition to pain chronicity [113,144,145]. This knowledge will be translated to the development of novel diagnostic kits that assess the risk an individual carries for developing chronic pain (if undergoing a surgery that carries significant morbidity for chronic postsurgical pain). Similar kits are expected to provide prognostic predictions that would enable caregivers to ‘tailor’ the best treatment choices an individual is expected to benefit from, based on his/her ‘genetic fingerprints’. These kits could also be used to better select subjects for clinical trials, thereby minimizing costs and shortening drug development times. New compounds would be developed that provide effective pre-, intra- and post-operative care, thereby preventing the outbreak of chronic postsurgical pain. Tagging the product of such genes with antibodies and carrying out immunohistological studies in animal models of chronic postsurgical pain could uncover new pain mechanisms and identify neuronal and/or glial cell types expressing chronic postsurgical pain genes, and their networks, some of which are currently unknown to us. Better rodent models that carry chronic postsurgical pain genes, relevant to human pain, could be developed and used as a platform to test the efficacy of novel drugs for chronic postsurgical pain. Finally, gene therapy would make it possible to patch ‘bad’ gene variants that carry the risk for chronic postsurgical pain. Judging by the rapid advancements in the Genome Project, this futuristic scenario may become a reality in our lifetime.

Preventive analgesia

As depicted in **FIGURE 1**, it is important to ascertain the precise mechanisms that underlie the relationship between pain at time one (e.g., preoperative pain or acute postoperative pain) and pain at time two (e.g., 1 year after surgery). The idea that pain is in some way etched into the CNS [108,146,147] has been at the heart of efforts to halt the transition to chronicity by blocking noxious perioperative impulses from reaching the CNS using a pre-emptive

or preventive pharmacological approach. However, if the relationship between acute postoperative pain and chronic pain is merely associative, and both are caused by one or more factors that themselves are inter-related, then no type or amount of blocking will prevent the development of chronic postsurgical pain.

Studies in a rodent model of PLP indicated that blocking afferent input from the surgical field at the time of nerve injury and shortly thereafter prevents chronic neuropathic pain-related behavior, while artificially prolonging it, especially in C-fibers, increases the chronic pain behavior [36,37,38,129,148–150]. This line of basic science research continues to introduce novel compounds (e.g., ralfinamide [150]) that show positive pre-emptive effects in rodent models of neuropathic pain and which could be tested as pre-emptive analgesics in humans. These findings have taken a long time to impact clinical practice and, as such, the management of acute postoperative pain has been dominated by an outdated concept of pain. Pain was viewed as the end product of a passive system that faithfully transmits a peripheral pain signal from nociceptors to a pain center in the brain. This view has resulted in a strategy for managing postoperative pain that is inadequate, in part because it treats the patient only after the pain is well established. Patients arrive in the postanesthetic care unit (recovery room) after surgery, often in extreme pain, where they receive multiple doses of analgesics in a short period of time in an effort to bring the pain down to a tolerable level [151,152]. However, basic science and clinical data show that brief, noxious inputs or frank injury that activates A- and mainly C-fibers (e.g., cutting skin, muscle or nerve fibers) induce long-lasting changes in central neural function that persist well after the offending stimulus has been removed or the injury has healed [40–42,44,104–107]. This view of pain, involving a dynamic relationship between peripheral and central mechanisms, is inconsistent with the archaic notion that pain results from transmission of impulses along a straight through, feed-forward pathway from a site of injury to the brain [153].

The practice of treating pain only after it has become well entrenched is slowly being replaced by a preventive approach that aims to block the transmission of the primary afferent injury discharge, the inflammatory response, and ensuing ectopic activity [154–157]. The intent behind this approach is not simply that it reduces nociception and stress during surgery – although these are also worthwhile objectives. The idea that acute postoperative pain might be intensified by a state of central neural hyperexcitability induced by surgery can be traced to Crile [158] and later to Wall [159], who suggested that ‘pre-emptive preoperative analgesia’ would block the induction of central neural sensitization brought about by incision and thus reduce acute postoperative pain intensity. Since its introduction, this concept has been refined, based in part on confirmatory and contradictory clinical evidence, developments in basic science and critical thought. The suggestion that surgical incision triggers central sensitization [159] has been expanded to include the sensitizing effects of preoperative noxious inputs and pain, other noxious intraoperative stimuli, as well as perioperative peripheral and central inflammatory mediators and ectopic neural activity [160].

The perioperative period can be divided into three distinct phases: pre-, intra- and post-operative. Specific factors within these phases contribute to the development of acute postoperative pain. These factors include: preoperative noxious inputs and pain; A- and C-fiber injury barrage resulting from the cutting of skin, muscle, nerve and bone, or wound retraction; and post-operative peripheral nociceptive input and input in low-threshold afferents, including that arising from the inflammatory response and ectopic neural activity in the case of nerve injury. Each of these factors can contribute to peripheral and central sensitization and each, therefore, can be targeted using a preventive approach. We propose that the relative contribution of these factors to acute postoperative pain is dependent on the surgical procedure, extent and nature of tissue damage, duration of surgery, timing of treatments relative to incision, pharmacokinetics of the agent(s) used preoperatively, presence or absence of additional analgesia intraoperatively, nature of postoperative analgesia and many other variables, including the genetic background that contributes a predisposition to be affected by any one of the parameters mentioned earlier. Minimizing the negative impact of as many as possible of these factors across the three perioperative phases will increase the likelihood of preventing the induction and maintenance of peripheral and central sensitization. Preventing sensitization will reduce pain and analgesic requirements [160].

In contrast to pre-emptive analgesia, which requires two groups of patients to receive identical treatment before or after the same type of incision or surgery [161], the focus of preventive analgesia is not on the relative timing of analgesic or anesthetic interventions, but on attenuating the impact of the peripheral nociceptive barrage associated with noxious preoperative, intraoperative and/or postoperative events/stimuli. The rationale for preventive analgesia is to capitalize on the combined effects of several analgesic agents, administered across the preoperative, intraoperative and postoperative periods, in reducing peripheral and central sensitization [160]. Therapeutic benefits associated with multimodal regimens include improved efficacy, lower doses and fewer adverse effects [162].

Preventive analgesia is demonstrated when postoperative pain and/or analgesic use are reduced beyond the clinical duration of action of the target agent, which has been defined as more than 5.5 half-lives of the target agent [160,163]. This requirement ensures

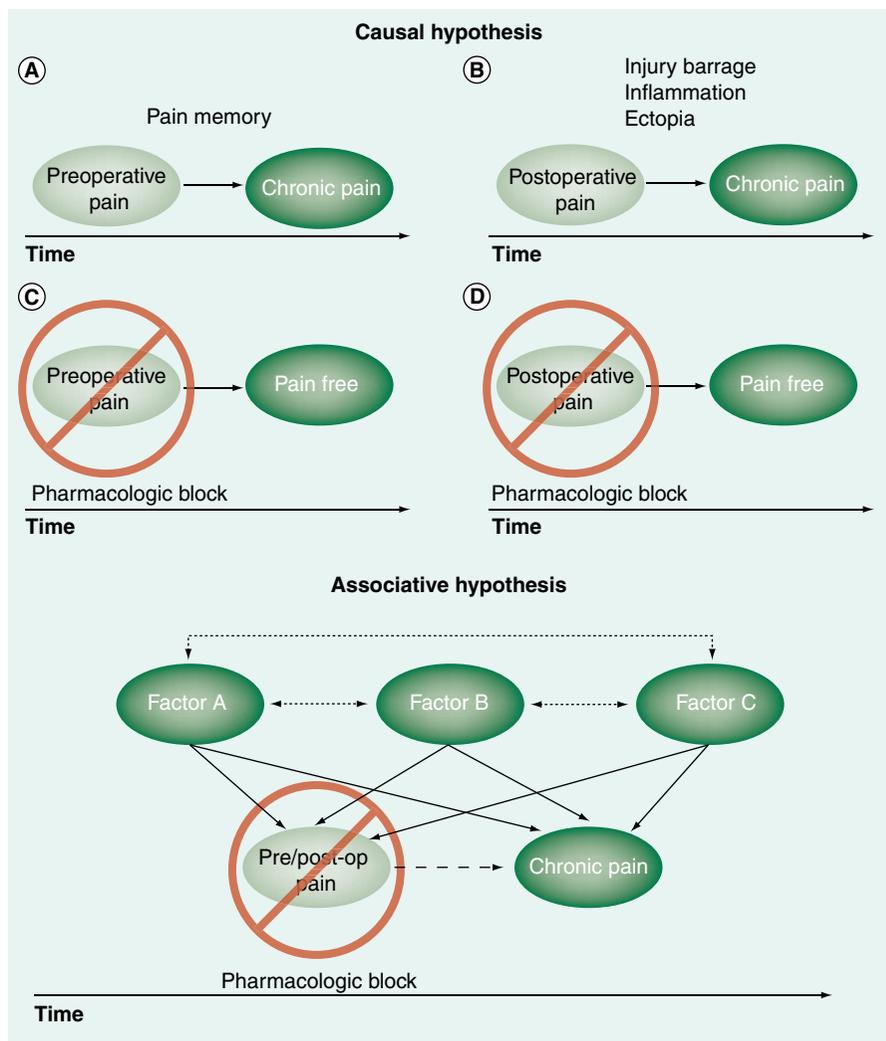


Figure 1. Causal (top) and associative (bottom) hypotheses predicting the prevention and nonprevention of chronic postsurgical pain by pharmacologic blockade at various times throughout the perioperative period. Top: transition to chronicity (A,B) may be prevented by pharmacological blockade of preoperative pain (C) and/or acute postoperative pain (D) assuming preoperative or acute postoperative pain are the causes of chronic postsurgical pain. Bottom: transition to chronicity will not be prevented if pains are merely associated and caused by one or more inter-related factors. post-op: Postoperation.

that the observed effects are not simply analgesic effects. A recent review of the preventive analgesia literature indicates that, across a variety of classes of agents, preventive analgesia reduces pain, analgesic consumption or both at a point in time that exceeds 5.5 half-lives of the target agent [160]. Although the evidence favors a preventive approach, relatively few studies have been designed to examine the possibility that chronic postsurgical pain can be prevented or attenuated, as reviewed later.

Postamputation PLP

A series of studies, beginning with the promising results of the nonrandomized study by Bach *et al.* [164], have examined the long-term benefits of perioperative epidural analgesia in reducing the incidence and intensity of PLP after limb amputation [165].

The initial promise, however, has not materialized. In what is perhaps the most methodologically sound study conducted on the topic to date, Nikolajsen *et al.* evaluated the long-term effects on phantom limb and stump pain of continuous epidural morphine and bupivacaine administered 18 h before, during and for approximately 1 week after lower limb amputation [166]. The control group received epidural saline before and throughout the surgical procedure followed by epidural morphine and bupivacaine postoperatively. There were no significant differences between the groups in pain incidence, intensity or opioid consumption at any time up to 12 months after surgery. Subsequent randomized, controlled studies using perioperative epidural bupivacaine and diamorphine [167], intrathecal bupivacaine and ketamine [168], intravenous ketamine for 3 days [169], epidural bupivacaine and ketamine for up to 3 days [168] have failed to find a significant long-term reduction in PLP incidence or intensity compared with placebo control conditions. Moreover, only one [170] of the three randomized, double-blind studies [170–172] conducted to evaluate the efficacy of oral gabapentin on already established PLP has shown a superiority of gabapentin over a placebo control condition.

The one recent positive study by Schley *et al.* compared two groups that underwent unilateral amputation ranging from removal of one finger to the entire forearm [173]. All amputees received postoperative analgesia by continuous brachial plexus anesthesia (ropivacaine 0.375% 5 ml/h) for 7 days. Thereafter, all participants could receive additional boli of ropivacaine 0.375% upon request. The main variable of difference between the groups was that for 4 weeks postamputation, one group received a daily dose of the NMDA receptor blocker memantine (20–30 mg) and the other group received placebo. During the first week post-amputation, the memantine-treated group needed significantly fewer local anesthetic blocks of the brachial plexus to relieve their pain. Moreover, at 4 weeks and 6 months after surgery, but not at 12 months, the memantine-treated group had significantly lower rates of PLP, and those with PLP reported lower pain intensity compared with the placebo group.

Several related issues require further study with regard to prevention of postamputation PLP:

It is important to distinguish between the effects of pre-amputation pain location, duration, frequency and intensity [108], and those of the surgical procedure (i.e., cutting of skin, muscle, bone, and ligation and transection of major nerve trunks) on the development of chronic PLP and stump pain [108]. To date, studies have not separately evaluated the nature, quality and intensity of preamputation pain versus acute postamputation pain. Other, more recent studies in nonamputee populations, have examined this issue as it pertains to the development of acute, as opposed to chronic, postsurgical pain. The data suggest that in the presence of presurgical pain, preoperative administration of analgesics does not lead to the anticipated lessening of postoperative pain or analgesic consumption, perhaps because central sensitization has already been established and the treatment could not reverse it. Postoperative pain and analgesic consumption were significantly reduced by pre- and intra-operative

epidural morphine, but not saline, for patients who did not report presurgical pain [174]. However, among patients with presurgical pain, pre- and intra-operative epidural morphine was no more effective than saline [174]. This raises the important issue of what effect blocking preoperative pain would have on the intensity of acute postoperative pain. A recent study of patients undergoing total hip arthroplasty showed that relief of preoperative pain by epidural ropivacaine for at least 12 h before surgery, followed by intraoperative epidural ropivacaine, reduced patient-controlled epidural anesthesia ropivacaine consumption 48 h after surgery compared with preoperative epidural saline and intraoperative epidural ropivacaine [175]. Based on these interesting and controversial findings, future studies should report on the presence (and duration) or absence of presurgical pain.

An important factor that has not received much attention is the distinction between preoperative pain related to the surgical procedure (i.e., in the anatomical region of the surgery, such as preoperative pain in the limb to be amputated) and pain that is unrelated to the surgical procedure (e.g., chronic lower back pain in a patient scheduled for posterolateral thoracotomy). A recent study of patients following radical prostatectomy found that patients were significantly at risk of developing chronic postsurgical pain whether or not the preoperative pain was related to the surgical site [90]. This distinction is important, not only to PLP after limb amputation, but to all surgeries, since these two situations may implicate different mechanism(s) underlying the development of chronic postsurgical pain.

A coexisting disease that affects peripheral nerve function may have contributed to the general lack of significant findings [176]. Likewise, such disease could have a deleterious effect on the neuroprotective capacity of the CNS to resist the excitotoxic impact of injury discharge. The vast majority of negative studies have recruited patients with diabetes and/or peripheral vascular disease, in contrast to the positive results found by Schley *et al.*, who studied individuals with acute trauma of the upper extremity requiring amputation [173].

Finally, further study is needed to improve the effectiveness of the perioperative blockade by using local anesthesia of peripheral nerves plus intrathecal analgesia. To date, the vast majority of negative studies have used epidural analgesia, which may not provide a sufficiently dense afferent blockade [177] to prevent central sensitization and rostral transmission of afferent input. Even a clinically effective blockade with intrathecal bupivacaine does not completely block nociceptive impulses from reaching the brain [178], suggesting that central sensitization might take place even with subclinical nociceptive inputs.

Postmastectomy pain

Recent evidence from well-controlled studies indicates that gabapentin, which binds to the α -2- δ subunit of the calcium channel ($\text{Ca}_v\alpha_2\text{-}\delta$ [179]), provides profound pain relief and opioid-sparing effects in the acute postoperative setting [180]. Two studies have focused on prevention of chronic postsurgical pain following breast surgery. Fassoulaki *et al.* randomized 50 patients undergoing breast cancer surgery to one of two groups using a

triple-dummy, double-blind design [181]. Patients in the multimodal treatment group received gabapentin (400 mg q6 h) starting the evening before surgery, transdermal eutectic mixture of local anesthetics (EMLA cream) beginning the day of surgery, and intraoperative ropivacaine irrigation of the brachial plexus and several intercostal spaces. Patients in the control group received placebos in place of the three active agents. After surgery, patients continued to receive gabapentin (400 mg) or placebo every 6 h for 8 days in addition to transdermal eutectic mixtures of local anesthetic cream or placebo cream daily for 3 days. At 3, but not 6, months after surgery, patients in the multimodal treatment group had a significantly lower incidence of axilla pain (14 vs 45%), arm pain (23 vs 59%) and analgesic use (0 vs 23%) compared with the placebo control patients.

These results contrast with an earlier randomized controlled trial by the same group using the same patient population [182]. Patients scheduled for breast surgery for cancer were randomly assigned to receive gabapentin (200 mg), mexiletine (400 mg) or placebo capsules three-times daily beginning the evening before surgery and continuing for 10 days after surgery. Although gabapentin proved to be significantly more effective than mexiletine or placebo in reducing acute movement-evoked pain intensity in the first 5 days after surgery, the 3-month follow-up failed to demonstrate a difference in the incidence or intensity of chronic pain. However, the incidence of burning pain was significantly lower in the two treatment groups compared with the placebo control group [182]. The failure to find a significant reduction in pain incidence or intensity at the follow-up may have been owing to an insufficient dose of gabapentin.

Iohom *et al.* compared the efficacy of a comprehensive, preventive multimodal analgesic regimen to a standard treatment in a randomized, nonblinded trial of 29 women undergoing surgery for breast cancer (mastectomy or breast tumor resection with axillary node clearance) [100]. Patients in the standard treatment group (Group S) received intramuscular morphine (0.1 mg/kg every 4 h), diclofenac suppositories (100 mg every 12 h) and dextropropoxyphene hydrochloride 32.5 mg plus oral acetaminophen 650 mg every 6 h for 48 h. Beginning 12 h before surgery, patients in Group N received intravenous parecoxib (a COX-2 inhibitor) 40 mg every 12 h followed by oral celecoxib (a COX-2 inhibitor) 200 mg until day 5 after surgery. In addition, before surgery, a paravertebral catheter was inserted and a continuous block established for up to 48 h after surgery with bupivacaine 0.25% (10 ml 12 hourly). Finally, patients in Group N also received oral acetaminophen 1 g every 6 h for 48 h. All patients received a general anesthetic for surgery. Pain intensity after movement was significantly lower in Group S compared with Group N across the 48-h study period. A telephone follow-up 2–3 months later, conducted by a blinded interviewer, showed a significantly lower incidence (and intensity) of chronic postoperative breast surgery pain in Group N (0%) than Group S (85%). While it is not possible to attribute the long-term prevention of pain specifically to COX-2 inhibition, these results do suggest that parecoxib and celecoxib contributed to the reduced incidence of chronic pain, consistent with evidence and predictions from the basic sciences [183].

Notwithstanding these positive effects, there have been serious concerns raised regarding the potential increased risk of cardiovascular thrombotic and myocardial events associated with the administration of COX-2 inhibitors [184–186] and, more generally, with nonselective NSAIDs [184].

Postradical prostatectomy pain

Gottschalk *et al.* conducted a randomized, double-blind study of 100 men undergoing radical retropubic prostatectomy [187]. Patients were assigned to one of the three groups to receive either preoperative epidural bupivacaine, epidural fentanyl or epidural saline followed by postoperative patient-controlled epidural analgesia with morphine and bupivacaine for all three groups. Acute pain intensity while in hospital was significantly lower in the two groups treated before incision compared with the saline control condition. Patients were followed up by telephone interview 3.5, 5.5 and 9.5 weeks after surgery. Activity scores 3.5, but not 5.5 or 9.5, weeks after surgery, were significantly higher than in the groups that received the epidural agents before and during surgery. The incidence of pain at 9.5, but not at 3.5 or 5.5, weeks after surgery was significantly lower in the groups that received the epidural agents before and during surgery compared with the control group. The authors concluded that the intraoperative administration of epidural fentanyl or bupivacaine significantly reduces the intensity of acute postoperative pain, pain incidence 9.5 weeks after surgery and is associated with higher activity levels postdischarge.

Katz *et al.* evaluated the short- and long-term effects of preoperative or postincisional intravenous fentanyl plus low-dose intravenous ketamine versus a standard treatment receiving intravenous fentanyl but not ketamine on postoperative pain and analgesic use in men undergoing radical prostatectomy under general anesthesia [188]. Pain scores and von Frey pain thresholds did not differ significantly among groups at any point in time during the first 3 days after surgery. Although day 3 cumulative patient-controlled analgesia (PCA) did not differ significantly among groups, on the third day after surgery the hourly rate of morphine consumption was significantly lower in the pretreated group compared with the two other groups. Follow-ups at 2 weeks and 6 months did not reveal significant group differences in pain incidence, intensity, disability or mental health. The addition of low-dose intravenous ketamine to a standard general anesthetic did not result in a clinically meaningful reduction in short-term pain or morphine consumption. Given the ineffective intervention, it is not surprising that there were no differences in the longer term.

Post-thoracotomy pain

Three studies have attempted to prevent the incidence and/or intensity of chronic pain after posterolateral thoracotomy with preoperative thoracic epidural analgesia [95,189,190]. Obata *et al.* compared the pre-emptive effects of administering a 72-h epidural infusion of a local anesthetic, mepivacaine, beginning before incision versus after completion of surgery in 70 patients scheduled to undergo thoracotomy [189]. Follow-up at 3 and

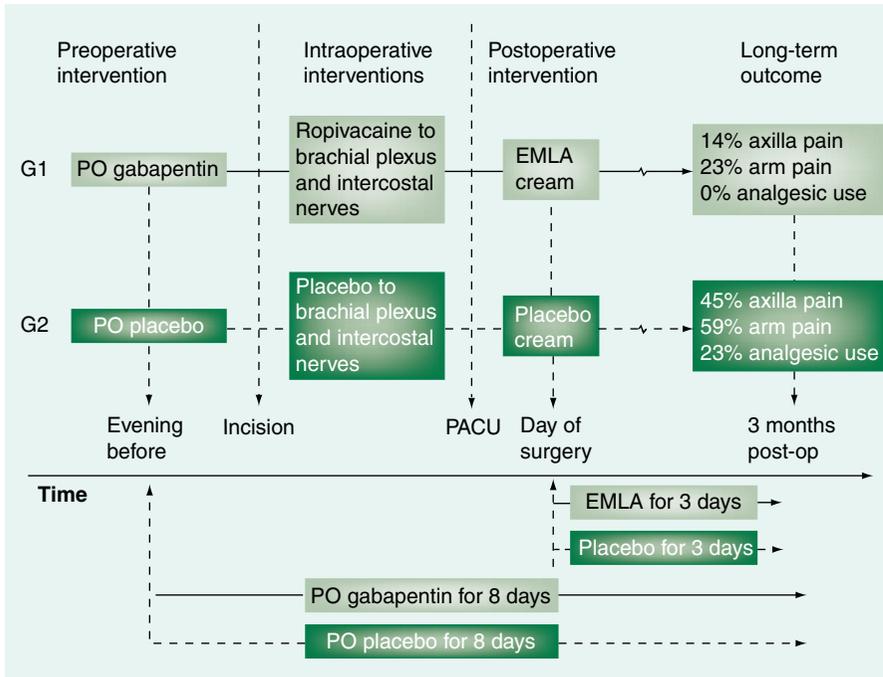


Figure 2. Illustration of the study by Fassoulaki *et al.* [181] examining the preventive effect of gabapentin (a $\text{Ca}_v\alpha_2\text{-}\delta$ ligand) in women undergoing breast cancer surgery.

EMLA: Eutectic mixture of local anesthetics; G: Group; PACU: Post-anesthetic care unit; PO: *per os*; post-op: Postoperation.

6 months showed a significant reduction in the incidence of chronic post-thoracotomy pain in the group of patients that received the epidural before surgery. These results were not confirmed by Ochroch *et al.* who randomly assigned 175 patients to receive thoracic epidural bupivacaine and fentanyl before incision or after rib approximation [190]. The incidence of chronic post-thoracotomy pain at 48 weeks did not differ significantly between the groups treated before versus after incision. Similarly, Senturk *et al.* randomized 69 patients scheduled to undergo thoracotomy to one of three groups: preoperative thoracic epidural bupivacaine and morphine followed by postoperative epidural PCA, postoperative epidural PCA with bupivacaine and morphine or postoperative intravenous PCA with morphine [95]. In contrast to the results of Obata *et al.*, there were no significant differences 6 months after surgery between the two epidural groups, but both showed a significantly lower incidence and intensity of chronic post-thoracotomy pain than the intravenous PCA group [189]. A more recent report examined the efficacy of gabapentin in reducing established post-thoracotomy pain [191] based on preliminary findings from a case series of patients with severe pain at least 4 weeks after thoracic surgery or trauma [192]. Patients were recruited into the trial if they had moderate-to-severe chronic post-thoracotomy pain (>5 on a 10 cm Visual Analogue Scale [VAS] and >12 on the Leeds Assessment of Neuropathic Symptoms and Signs [LANSS]) of at least 3 months duration that had proved refractory to earlier treatment and were assigned to receive either gabapentin or sodium naproxen (a nonselective NSAID) [191]. At the end of the

60-day treatment period, the percentage of patients that still had severe pain was reduced significantly in the gabapentin group (15%) compared with the naproxen group (~85%). Although these two studies were not randomized or blinded, they point to the next logical step of administering gabapentin before surgery and for several months following surgery in an attempt to prevent the development of chronic post-thoracotomy pain.

Chronic pain after iliac crest bone graft harvest

Iliac bone graft harvest for spinal fusion results in significant morbidity, including functional impairment, as well as severe pain at the harvest site in approximately 3% of patients [193]. Two small scale, randomized, controlled, double-blind studies have attempted to prevent chronic bone graft harvest site pain with multiple injections of bupivacaine or bupivacaine and morphine into the harvest site beginning 10 min after the start of surgery [194] and a 48-h continuous infusion of bupivacaine into the harvest site beginning at the time

of wound closure after procurement of the graft [195]. Both studies found a significant reduction in acute postoperative harvest-site pain and analgesic consumption, indicating that the interventions were efficacious. By 12 weeks after surgery the incidence of harvest-site pain was significantly lower in the bupivacaine plus morphine treated patients (none out of 15) than the saline control group (five out of 15) [196]. In the other study, a 4-year follow-up showed that chronic pain was not present in any of the nine bupivacaine-treated patients and was present in seven out of the ten saline controls [195]. Replication of these results with a larger sample size is required. These studies suggest that preventive analgesia can be achieved even when the analgesic intervention is started after incision and bone graft harvest (i.e., in the context of an unchecked peripheral nociceptive injury barrage during surgery).

Long-term pain after major abdominal-gynecological surgery

Katz *et al.* evaluated the short- and long-term preventive effect of perioperative administration of intravenous alfentanil for women scheduled for abdominal hysterectomy performed under general anesthesia [196]. In total, 45 patients were randomly assigned to one of three groups in a double-blinded manner to receive no alfentanil, low-dose alfentanil (30 $\mu\text{g}/\text{kg}$ at induction followed by intraoperative bolus doses of alfentanil 10–20 μg) or high-dose alfentanil (100 $\mu\text{g}/\text{kg}$ at induction followed by an intraoperative infusion of alfentanil 1–2 $\mu\text{g}/\text{kg}/\text{min}$) before and during surgery. The results showed that, although a composite measure of pain and morphine consumption was significantly lower in the

high- versus low-dose group up to 6 h after surgery, and significantly lower than the no dose group up to 12 h, these results were not clinically meaningful. A 6-month telephone follow-up did not reveal any significant differences among groups in pain incidence or severity. The authors conclude that surgical procedures carried out under general anesthesia alone using standard doses of opioids intraoperatively provide suboptimal protection from the injury barrage brought about by incision and subsequent noxious surgical events.

In another randomized, controlled, double-blind, study of 141 women undergoing abdominal gynecological surgery by laparotomy, Katz *et al.* found that preincisional, but not postincisional, administration of epidural lidocaine and fentanyl was associated with a significantly lower rate of morphine and reduced secondary mechanical hyperalgesia 48 h after surgery compared with a standard treatment group that received a sham epidural [197]. Follow-up at 3 weeks showed that pain disability ratings were significantly lower in the two groups that received the active epidural when compared with the standard treatment group, but no intergroup differences in pain, pain disability or general mental health were found at the 6-month follow-up [198].

Long-term pain after thyroidectomy

Brogly *et al.* evaluated the preventive effect of a single preoperative dose of gabapentin 1200 mg versus placebo in a randomized, controlled, double-blind trial of 50 patients undergoing thyroidectomy under general anesthesia [199]. All patients received a bilateral superficial cervical plexus block with ropivacaine and clonidine after induction of the general anesthetic. Neither acute pain scores at rest, nor after swallowing, nor analgesic consumption, differed significantly between the groups across the 24-h study period. However, 6 months after surgery, in a follow-up mail survey, the authors found that the incidence of neuropathic pain complaints was significantly lower in the patients that received preoperative gabapentin (4.3%) than placebo (29.2%). The delayed effect of gabapentin is difficult to explain in the absence of a similar effect in the acute postoperative period when the drug was active. The authors suggest that the absence of an early effect of gabapentin may have been masked by the bilateral superficial cervical plexus block.

Long-term pain after major digestive surgery

Lavand'homme *et al.* randomly assigned 85 patients undergoing major digestive surgery to one of four groups to assess the preventive analgesic effects of administering a local anesthetic (lidocaine or bupivacaine), an opioid (sufentanil or morphine) and an α_2 adrenergic agonist (clonidine) by the intravenous or epidural route, before and/or after surgery under general anesthesia [200]. Patients received the three agents by the intravenous (Group 1) or epidural (Group 3) route before surgery and immediately after recovery for 72 h, the intravenous route followed the epidural route (Group 2) or the epidural route followed by the intravenous route (Group 4). All patients also received a bolus dose plus infusion of low dose ketamine, which was started before incision and maintained throughout the procedure. Postoperative analgesics

were delivered by an intravenous or epidural PCA pump. The results showed that across the 72-h study period, the number of patient-controlled requests for postoperative analgesia and pain scores at rest, after movement and after coughing were significantly higher in Group 1 compared with the three other groups. The area of secondary mechanical hyperalgesia to punctuate stimulation surrounding the incision showed the same pattern of results: the groups that received the epidural, whether before, after, or before and after surgery, showed a smaller area of hyperalgesia than the group that received the agents by the intravenous route before and after surgery. Patients were followed up by telephone and mail survey 2 weeks, 1, 6 and 12 months after surgery. The incidence of chronic postsurgical pain in Group 1 at the 6- (48%) and 12- (28%) month follow-ups was significantly greater than the zero incidence in Groups 3 and 4 at both time points. The 12-month results suggest a greater contribution to chronic pain of noxious intraoperative versus postoperative afferent input given the findings that the incidence of chronic pain in Group 2 was neither different from that of Group 4 nor Group 1. Overall, the long-term results point to the importance of perioperative nociceptive blockade by the epidural route in preventing chronic postsurgical pain after major digestive surgery.

Taken together, the results from the studies of preventive multimodal analgesia are equivocal. While there is some evidence that chronic postsurgical pain can be minimized or prevented by an analgesic approach involving aggressive perioperative multimodal treatment, other studies fail to show this benefit. A careful examination of these results raises several related issues that we must address, which are now discussed.

The results show significant reductions in the incidence and/or mean intensity of long-term pain problems in some cases. However, a preventive analgesic approach does not work for everyone and, at present, we do not know for whom such an approach is effective. One might assume that the mechanisms underlying the interindividual differences in efficacy of preventive analgesia is controlled genetically. When these determinants are identified, it might be possible to extend the efficacy of preventive analgesia for certain individuals.

We also do not know the mechanism(s) by which chronic postsurgical pain is reduced when preventive analgesia is effective. The early pain relieving effects can be attributed to the pharmacological action of the agents used preventively; however, by definition [155,160,163] for studies that compare an active agent with a placebo control condition, preventive analgesia requires that the reduction in analgesic consumption and pain be observed at a point in time that exceeds the clinical duration of action of the target agent used preventively. This is meant to rule out the possibility that the observed effect is simply an analgesic effect. The typical explanation for a prolonged effect is that the agent(s) prevented (obtunded) the injury discharge, and/or peripheral and/or central sensitization and, thereby, reduced long-term pain. However, there really is very little good evidence that this is in fact the case, since we do not have accurate measures of sensitization in humans, and even if we did, this still would not indicate that reduction in sensitization is responsible for the long-term reductions in pain incidence

and/or intensity. The longer the time from the administration of the analgesic agent(s), the greater the probability that other factors contribute to the long-term effects. For example, in discussing the effectiveness of perioperative epidural analgesia versus a sham epidural in reducing pain disability scores, but not pain intensity scores, 3 weeks after surgery [197], Katz and Cohen suggested that the reduced hyperalgesia and rate of morphine consumption within the first 2 days after surgery afforded the epidural groups a 'head start' in terms of comfort level and recovery compared with the sham epidural group, possibly increasing their self-efficacy in dealing with pain or in mobilization [198]. A similar finding has been reported with respect to activity levels 3.5 weeks after radical retro-pubic prostatectomy [187]. In that study, activity levels but not pain intensity were significantly higher in patients who had received pre-emptive epidural bupivacaine or fentanyl. Thus, the mechanisms underlying preventive analgesia are probably more varied than currently acknowledged.

We do not know why preventive analgesia does not work in some patients. One explanation that has not been investigated is that for some patients, the drug dose simply may not be large enough or changes in the kinetics or dynamics of the drug under investigation may have an impact on the results. Another possibility is that preoperative pain interferes with the effectiveness of preventive analgesia, perhaps because central sensitization has already been established [15,164,174,175]. Finally, genetic differences are also likely to play a role, in that study groups may have included a variable mixture of individuals susceptible or resistant to the potential pre-emptive effect of the studied treatment, thereby masking a real effect.

Chronic pain is a complex experience that manifests in several major domains, which include sensory–discriminative, affective–aversive and cognitive–evaluative. Each domain comprises several subdomains, for example, the sensory–discriminative domain consists of pain intensity (ranging from the lowest to

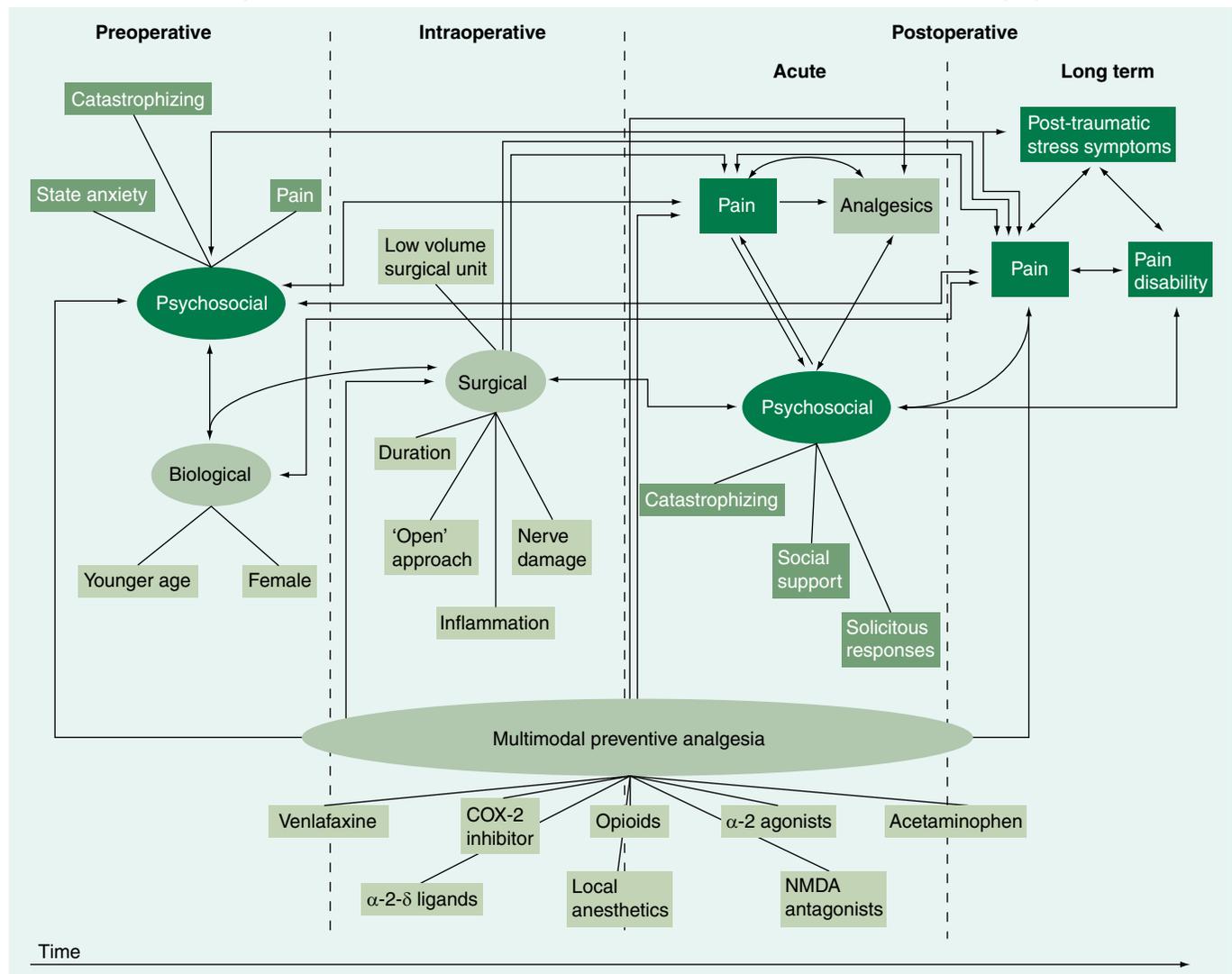


Figure 3. Schematic illustration of the processes involved in the development of chronic postsurgical pain and pain disability showing relationships (arrows) among preoperative, intraoperative and postoperative factors. Lines with double arrows between variables show associative relationships reported in the literature. Lines with a single arrowhead show causal relationships based on randomized controlled trials of preventive analgesia.

the maximal; typical intensity), pain location (is it felt in the surgical field and/or can spread 'extraterritorially' to areas not innervated by injured nerves, can be felt as 'mirror image' pain on the contralateral intact side as well), pain quality (e.g., burning, crushing and electrical shock-like) and temporal (episodic or constant; if episodic, the frequency and duration of episodes is essential to document) subdomains. Similar breakdown into subdomains can be demonstrated for the affective-emotive and cognitive-evaluative dimensions. It is well established that parts of the brain that process sensory-discriminative aspects of the pain are largely separate from those that process affective-aversive aspects (e.g., S1 and S2 cortices and limbic areas, respectively). Moreover, each aspect largely engages unique biochemistry and targets for drugs including, presumably, those relevant for preventive treatments. However, the main outcome measures in the vast majority of randomized controlled trials are simply pain intensity and/or presence/absence of pain and analgesic use. While there is some correlation between pain intensity and the aversive-affective aspects of the pain, this correlation is not very tight and the intensity cannot be taken as the sole parameter for the complex experience that pain is, especially when it has become chronic. It is rare to find a study that is more comprehensive in the outcome measures assessed. Of particular relevance to chronic postsurgical pain is the tendency for the anesthesia literature to focus on outcome measures of pain and analgesic use, and the psychological literature to focus on measures of pain disability or pain interference, making cross-study comparisons difficult. Recommendations for assessment of core measures and domains in clinical trials [201] include relevant psychological, emotional and physical-functional variables, in addition to those routinely assessed (i.e., pain and analgesic use). Assessment of additional domains of functioning may help to shed light on the predictors of severe acute postoperative pain, the processes involved in recovery from surgery and the risk factors for developing chronic postsurgical pain [198].

Expert commentary

As depicted in FIGURE 3, the transition of acute postoperative pain to pathological chronic postsurgical pain is a complex developmental process involving biological, psychological and social-environmental factors across the three phases of the perioperative period (preoperative, intraoperative and postoperative). The noxious effects of surgery (e.g., arising from incision, retraction, inflammatory response, ectopic activity following nerve injury and CNS reorganization into a centrally sensitized state), in conjunction with the competing, beneficial effects of perioperative, preventive multimodal analgesia, interact with pre-existing and concurrent pain, psychological and emotional factors (e.g., catastrophizing and pain coping strategies), as well as the social environment (e.g., solicitousness and social support) to determine the nature, severity, frequency and duration of chronic postsurgical pain. Effectiveness of psychological management programs for other chronic pain problems is well established, but prevention and treatment efforts for chronic postsurgical pain have lagged behind. Development of a truly multimodal treatment regimen

is essential, including not only modification of known surgical risk factors and protective pharmacotherapy, but also provision of perioperative psychological pain management programs aimed at preventing and treating chronic postsurgical pain. We are, at present, a long way from being able to predict with certainty who will recover uneventfully and who will go on to develop debilitating chronic pain. Finally, pain genetics carries the hope that such a reality can be achieved in our lifetime.

Five-year view

We do not expect significant gains to be made in the prevention of chronic postsurgical pain within the next 5 years. However, with the relatively recent introduction, and perioperative use, of the COX-2 inhibitors and the $\text{Ca}_v\alpha_2\text{-}\delta$ ligands, gabapentin and pregabalin, we may begin to see evidence of a reduction in the incidence and intensity of certain chronic postsurgical pains when used in combination with other agents in a balanced regimen of multimodal analgesia. Since these agents are available for oral administration, patients can be discharged with orders to continue to take them for several weeks after surgery, thus providing the opportunity for prolonged inhibition of the inflammatory cascade and suppression of ectopic activity. Both the COX-2 inhibitors and the $\text{Ca}_v\alpha_2\text{-}\delta$ ligands have been shown to produce clinically significant reductions in pain and opioid requirements in the acute postoperative setting and a logical extension would be to provide ongoing treatment with these agents to help minimize the transition to pain chronicity. We anticipate that some progress will be made in identifying heretofore unknown psychosocial predictors of chronic postsurgical pain and, hopefully, we will see the beginnings of psychological treatments aimed both at preventing chronic postsurgical pain and better managing it once it has developed. Clinically relevant behavioral mouse and rat models are available for the study of mechanisms underlying acute and chronic postsurgical pain and they can be used as platforms for research and development of the next generation of analgesics, such as ralfinamide, that shows pre-emptive analgesic efficacy in rodent models. A very promising new research field that lags behind research into other human diseases is pain genetics. Powerful genetic assays are available to identify the genes controlling the interindividual variability in developing such pain types, as well as the variance in the efficacy of preventive and palliative analgesia. In the coming 5 years, we should see the first signs of the 'genetic revolution' in pain medicine that will identify novel treatment targets.

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Key issues

- Very few studies define chronic postsurgical pain. The absence of an operational definition of chronic postsurgical pain has hindered progress in epidemiological and clinical research, making cross-study comparisons difficult and partly explaining the large variability in estimates of chronic postsurgical pain and the efficacy of pre-emptive analgesia on this type of pain.
- Notwithstanding these obstacles, severe chronic postsurgical pain occurs in up to 10% of patients.
- Surgical procedures with the greatest incidence of chronic postsurgical pain are associated with intentional or unintentional nerve damage, such as limb amputation, mastectomy and posterolateral thoracotomy. The incidence of chronic pain after these surgical procedures ranges between approximately 60 and 70%.
- Avoiding nerve damage during surgery will undoubtedly reduce the incidence of chronic postsurgical pain.
- The most consistent risk factor for chronic postsurgical pain is the presence and/or intensity of prior pain, experienced either preoperatively or early postoperative pain experienced in the days and weeks after surgery. One of the most important issues is to determine whether the relationship between prior pain, early postoperative pain and chronic postsurgical pain is causal, associative or a combination of the two.
- Perioperative, multimodal preventive analgesia regimens have been shown to protect against the development of chronic postsurgical pain and to the incidence and/or the intensity of chronic postsurgical pain.
- Preliminary data indicate that psychological and social–environmental risk factors are associated with the development of chronic postsurgical pain, but we do not know whether these effects are associative or causal.
- Psychological prevention and treatment efforts for chronic postsurgical pain have lagged behind other chronic pain disorders. Development of perioperative psychological pain management programs aimed at preventing and treating chronic postsurgical pain is essential.
- A big hope for pain medicine lies in genetics. However, the genetics of chronic postsurgical pain cannot advance without the availability of cohorts for study, comprising DNA samples of individuals with a comprehensive characterization of their acute and chronic postsurgical pain phenotypes, previous life experiences with pain and a detailed medical case history. There are currently no such cohorts available for study, although the genetic methodologies are at hand. It is essential to create multicenter research teams to collect such cohorts.

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