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REVIEW ARTICLE/BRIEF REVIEW

Post-surgical pain syndromes: a review for the non-pain specialist

Les syndromes douloureux postchirurgicaux: une synthèse pour le non-spécialiste de la douleur

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Abstract

Purpose *This is a selective narrative review of the latest information about the epidemiology, impact, and prevention of chronic post-surgical pain (CPSP), intended primarily for those without a special interest in pain medicine.*

Principal findings *Chronic post-surgical pain is an important problem in terms of personal impact. It has staggering economic implications, exerts powerful negative effects on the quality of life of many of those it afflicts, and places a significant burden on chronic pain treatment services in general. It is well known that surgery at certain body sites is apt to cause CPSP, but emerging evidence shows a strong correlation between CPSP and demographic (young age, obesity, and female sex) and psychological characteristics (anxiety, depression, stress, and catastrophizing). Severe acute pain is a strong risk factor for CPSP, and this adds yet more weight to the argument that acute pain should be controlled effectively. In specific circumstances, CPSP can be reduced by regional anesthetic techniques, infiltration of local anesthetic, or preoperative use of gabapentin. The ability of other known interrupters of afferent nociceptive transmission—commonly used to reduce CPSP when administered at the time of surgery—is currently unproven, as is the hypothesis that the use of remifentanil during surgery worsens CPSP.*

Conclusions *Reduction of CPSP is a worthy long-term outcome for anesthesia providers to consider as they plan the perioperative care of their patients. More evidence is needed about the effect of currently used analgesics and other perioperative techniques on CPSP.*

Résumé

Objectif *Voici un article de synthèse narratif et sélectif des connaissances les plus récentes concernant l'épidémiologie, l'impact et la prévention de la douleur chronique postchirurgicale (DCPC), qui s'adresse principalement aux personnes n'ayant pas d'intérêt particulier pour la médecine de la douleur.*

Constatations principales *La douleur chronique postchirurgicale est un problème important en termes d'impact personnel. Elle a des implications économiques dramatiques, exerce des effets négatifs puissants sur la qualité de vie de bon nombre des personnes qu'elle affecte, et constitue un fardeau considérable pour les services de traitement de la douleur chronique en général. Il est bien connu que la chirurgie pratiquée sur certaines parties du corps prédispose à une DCPC, mais de nouvelles données probantes montrent une importante corrélation entre la DCPC et certaines caractéristiques démographiques (jeune âge, obésité et sexe féminin) et psychologiques (anxiété, dépression, stress et catastrophisation). La douleur aiguë grave est un important facteur de risque de DCPC, et cela ajoute encore du poids à l'argument selon lequel la douleur aiguë devrait être contrôlée efficacement. Dans des circonstances spécifiques, la DCPC peut être réduite grâce à des techniques d'anesthésie régionale, à l'infiltration d'anesthésique local ou à l'utilisation préopératoire de gabapentine. La capacité d'autres 'interrupteurs' connus de la transmission nociceptive afférente – communément utilisés pour réduire la DCPC lorsqu'ils sont administrés au moment de la chirurgie – est actuellement inconnue, et l'hypothèse selon*

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laquelle l'utilisation de rémifentanil pendant une chirurgie augmenterait la DCPC reste à prouver.

Conclusion *La réduction de la DCPC est un pronostic à long terme qu'il vaut la peine de prendre en compte lorsque les professionnels en anesthésie planifient les soins périopératoires de leurs patients. Des données probantes supplémentaires sont nécessaires quant aux effets sur la DCPC des analgésiques et autres techniques périopératoires utilisés actuellement.*

Chronic pain is a common condition that significantly worsens the quality of life of the people it afflicts.[1] It is almost always incurable, and supportive treatment is expensive and hard to obtain in most parts of Canada and many other nations.[2] Consequently, the idea of preventing it is even more attractive than for other chronic conditions. In most cases, the onset of a chronic pain complaint is either gradual (e.g., fibromyalgia) or sudden but unpredictable (e.g., nerve injury from trauma). In chronic post-surgical pain (CPSP), however, the onset and magnitude of tissue damage can be timed and controlled within some limits. This possibility offers an opportunity to intervene to prevent chronic pain when effective interventions are available.

Anesthesiologists find themselves in the forefront of this effort in both laboratory and clinical settings. As the mandate of the specialty widens, it behooves every anesthesia provider to have a working knowledge of CPSP and to understand the ways in which it might be predicted, prevented, or even worsened.

For this narrative review, we searched MEDLINE® in April 2013 using the term "Chronic Post Surgical Pain". We then followed the established trail to find relevant original research articles and topic reviews in English and supplemented this material with citations from the works themselves.

Definition

There is no universally accepted definition of CPSP. Conceptually, it requires persistent pain after the point when all putatively painful surgical tissue disruption has healed. In practice, a variety of time-based definitions are used, ranging from one month to one year after surgery, with an informal consensus of two months.[3]

Incidence and prevalence

A gross but easily remembered oversimplification of the available data is that one in five of those who undergo surgery will go on to experience persistent pain at the surgical site.[4] This staggering statistic should give everyone pause for thought, as this is about the same rate as perioperative venous thromboembolism[5] and four times the average rate of surgical wound infection.[6] Patients are explicitly warned about these two complications of surgery wherein invasive and potentially harmful preventive measures are (rightly) deemed appropriate. Surgeons and anesthesiologists have been unaware of the magnitude of this problem for most of modern surgical history. Indeed, the proper study of CPSP was hampered for many years by sociologically fascinating influences on the interaction between patients and surgeons (as well as other doctors) that resulted in downplaying reports of pain intensity at follow-up visits in an attempt to please the doctor.[7] Surveys, particularly of the community-based variety, yield much better data, and excellent recent examples are available.[8] The incidence of CPSP varies reproducibly between surgical sites, although exact comparisons between studies of the same operation are somewhat confounded by variations in definition and measurement technique. Nonetheless, conservative estimates of CPSP risk for the top four most affected surgical sites are: chest wall 35%, breast 31%, total joint arthroplasty 20%, and iliac crest bone harvest 19%.[4] Chronic post-surgical pain has been reported in almost all types of surgery and is not confined to major procedures. For example, open inguinal hernia repair carries a 7% risk of CPSP.[4] A distinction is generally made between CPSP in the current sense and chronic pain following unsuccessful surgery for painful pathology, such as radiculopathy.

On a population basis, CPSP accounts for a significant portion of chronic pain in general. In a previously cited cross-sectional community sample from Norway in 2012,[8] CPSP accounted for 33% of all cases of chronic pain in the sample, while a study from the United Kingdom in 1998 identified surgery as an antecedent in 22.5% of attendees to a pain clinic.[9]

Etiology

Chronic post-surgical pain begins as acute post-surgical pain, which is a near-universal experience. The mechanism by which CPSP is then generated is the subject of much research, mostly in animal models. Theories abound, but hard evidence in humans is scant.[10] We know that sensitization of the peripheral and central nervous system plays a crucial part in the genesis of all chronic pain following injury, and CPSP is no exception.[11] Most, but not all cases of CPSP are associated with sensory abnormalities in or around the incision.[8] Hyperesthesia and hypoesthesia are both associated with CPSP. The obverse is not true;

persistent sensory abnormalities may follow surgery without being painful.[8] This undermines the theory that CPSP is simply an error of heightened afferent noxious input to the cortex. Nerve injury, while strongly associated with CPSP, is not sufficient to cause the condition by itself. Most lines of evidence from both laboratory and clinical viewpoints seem to lead to a theory of a complex series of perturbations in the way that wind-up of the nervous system is turned off after the acute phase, associated with leading roles for higher cognitive functions in the process, influencing events at the spinal cord by powerful descending control mechanisms.[11] While increased knowledge of the mechanics of nociception has led to the development of meaningful tools for ameliorating acute pain (such as intraspinal opioid delivery),[12] it is disappointing to reflect on the fact that it has yet to do so for CPSP.

Part of the answer to the conundrum of CPSP may lie in the fact that it has become recognized only recently as being a multisystem illness that transcends the operative field and includes, most importantly, the patient's psychological state and social circumstances. There is compelling evidence that constructs such as anxiety, depression, and catastrophizing, increase the risk of CPSP.[13] Those who have preoperative chronic pain distant from the surgical site are more likely to develop CPSP, and when they do, they are more likely to find it disabling.

Impact

All surgical patients accept that they will have a scar, so why shouldn't we simply accept mild persistent pain as another inevitable part of the price of surgical intervention? First, CPSP is seldom mild. Three years after surgery, pain was moderately severe in 12% and severe in 7% of those who reported CPSP.[8] Second, CPSP has significant impact on quality of life. In a prospective Canadian study of 76 people undergoing general surgery, about one-third reported pain-related interference with mood, sleep, and quality of life at six months postoperatively.[14] This was found to be the case despite aggressive perioperative analgesia with apparently good results at the time. A larger retrospective analysis using data from the Swedish Hernia Register recorded pain-related interference with basic activities of daily living, work, or sports in 5-6% of cases.[15] Those with CPSP following total joint arthroplasty have a significantly worse quality of life—as measured using the Short Form Health Survey (SF-36®)—than those who do not.[16] Data are lacking to support the contention that these are risks that surgical patients knowingly undertake. In fairness, equally unknown is the degree of risk of adverse effects that patients would be willing to accept from measures put in place to try to reduce the risk of CPSP.[17]

Prevention

Clinicians seeking to mitigate the risks of CPSP must rely on a multi-faceted approach at several levels of the surgical process.

The first tactic, chronologically speaking, falls to the surgeon. All surgery carries the risk of CPSP, but not all surgery is medically necessary. For example, the patient contemplating augmentation mammoplasty ought to be aware of a greater than 40% risk of CPSP at three years, with a 10% chance of this being moderate or severe and a 6% chance of pain being the reason for regretting the operation.[18] Chronic post-surgical pain following vasectomy is rare, but the high volume of these procedures results in a relatively large number of cases.[19] No anesthesia provider would intentionally seek to undermine the relationship between surgeon and patient, but sound knowledge of the literature in this regard, if tactfully deployed, could enhance the quality of the consent process in certain circumstances.

At first preoperative contact, anesthesia providers could systematically quantify the risk of CPSP using a questionnaire-based assessment tool. Few institutions do this, even our own. Identification of those at highest risk for CPSP could then be used to target surveillance and intervention to greatest effect. Similar tools exist for the prediction of acute postoperative pain[20] and, unsurprisingly, there is plenty of overlap between risk factors for both entities. These assessment tools are derived from case series in which many putative risk factors are analyzed by logistic regression to extract independent predictors with which to create a scoring system. As with prediction aids from other areas of medicine, these tools are imperfect, since compromises are necessary in order to minimize false positives and negatives. One such CPSP risk assessment tool[21] is described in Table 1. There is a linear relationship between the number of positive responses to each of the five constructs and the risk of CPSP, with those scoring ≥ 4 having a risk of $> 70\%$. It is noteworthy that all of these independent predictors of CPSP are attributes of the person themselves rather than technical characteristics of anesthesia or surgery. This preeminence of psychological factors in predicting CPSP is echoed in a comprehensive review of the subject in 2009,[22] in which the strongest correlates of CPSP in a variety of surgical models were depression, psychological vulnerability, stress, and delayed return to work, although the latter is clearly an effect and not a risk. Younger adults

Table 1 Perioperative predictive risk factors for chronic post-surgical pain (CPSP)[21]

Construct	Score
"Capacity overload" in the six months prior to surgery (having had more to deal with in the psychological sense than the subject thought (s)he could handle)	1
Preoperative pain in the body part to be operated on	1
Preoperative pain distant from the operative site	1
The presence of two or more indicators suggestive of stress (sleep disorder, exhaustibility/exhaustion, frightening thoughts, dizziness, tachycardia, feeling of being misunderstood, trembling hands, or taking sedatives or sleeping pills)	1
An average pain score > 5/10 on days 1-5 postoperatively	1
Points are added to render a score from 0-5. Score correlates with CPSP risk as follows: 0 = 12%, 1 = 30%, 2 = 37%, 3 = 68%, 4 = 82%, 5 = 71%.	

Adapted from reference [21]: *Althaus A, Hinrichs-Rocker A, Chapman R, et al.* Development of a risk index for the prediction of chronic post-surgical pain. Eur J Pain 2012; 16: 901-10

are at higher risk of CPSP than older adults,[20] but children seem to be less susceptible than adults.[23]

Pain predicts pain,[10] whether from preoperative to postoperative, postoperative to CPSP, or, most importantly, from preoperative to CPSP. Once the risk of CPSP has been assessed, the next most pressing need is effective management of any existing preoperative pain. This is separate from the idea of preventive (formerly "preemptive")[24] analgesia, in which analgesic interventions are applied before or during surgery to patients who may not necessarily have pain at the time. Perhaps the efficacy of aggressive analgesia in preventing CPSP has best been shown in the vascular anesthesia literature on lower limb amputation.[25] Early studies in the area were driven by the seductive idea that regional anesthetic blockade would lead to an elimination of phantom limb pain by preventing wind-up of secondary afferents in the dorsal horn of the spinal cord. When this failed to be the envisioned panacea, enthusiasm waned somewhat. More recently, however, it has been shown that effective pre-amputation pain control reduces risk of CPSP—notwithstanding some reservations about the design of the studies concerned—and it is not important whether that is achieved with neuraxial blockade or intravenous opioids.[26]

Some surgical factors are known to have significant impacts on the risk of CPSP. While these are not generally within the control of the anesthesia provider, knowledge of these factors may contribute to planning anesthesia strategies against CPSP. Operations performed in units with high throughput of similar cases are less apt to be associated with CPSP than those performed in less busy centres.[27] Minimally invasive surgery probably, but not unequivocally, reduces risk of CPSP, as exemplified by a large randomized controlled trial (RCT) which showed that laparoscopic inguinal hernia repair reduces risk of CPSP by 60% compared with open surgery.[28] Long operations (more than three hours) are more likely to be associated with CPSP than shorter ones.[29] Given the common finding of sensory abnormalities on neurological examination in CPSP, much attention has been given to nerve protection in the surgical field.[30] Most studies have found benefit from such approaches, but some have not.[31]

On the day of surgery itself, particularly when faced with a patient at high *a priori* risk of CPSP, the anesthesia provider naturally wonders whether the anesthetic technique should be modified for this reason. There are some areas in which the extant literature can be helpful in this regard, but, regrettably, there are many more where it currently cannot.

Regional anesthesia techniques have been extensively studied.[32] A link can easily be imagined between some of the factors known to increase CPSP, such as anxiety and a reluctance to undergo surgery awake or to submit to more awake percutaneous procedures than are absolutely essential. For this reason, non-randomized comparisons of regional *vs* general anesthesia for CPSP should be interpreted with great care. Results of randomized studies have shown that epidural analgesia decreases CPSP after thoracotomy[33] and extensive midline laparotomy,[34] and paravertebral blockade does so after breast cancer surgery.[35] There is also support for simpler interventions, such as wound infiltration,[36,37] continuous instillation of local anesthetic into wound catheters,[38] and intraperitoneal instillation of local anesthetic following Cesarean delivery.[39] There is also solid literature on the benefits of regional anesthesia on acute post-surgical pain intensity.[40] While the majority of those studies were not designed to follow their subjects beyond the immediate postoperative period, it makes sense that some of these effects might be advantageous in the long term, since high acute postoperative pain intensity is a strong predictor of CPSP. A pragmatist might take the view that a regional anesthesia or analgesia technique or supplement is a good strategy when CPSP risks are high and a plausible block approach exists. That risk might be high because of patient factors, the type of surgery planned, or both. Failing that, infiltration or instillation of local anesthetic is a worthwhile expedient and should be encouraged whenever possible. At the very least, such interventions will decrease acute postoperative pain, which is an end in itself. The regional anesthesia cynic, on the other hand, will point to the rare but devastating specter of permanent iatrogenic nerve injury and hold this up as an example of a CPSP prevention strategy causing the very thing it was intended to prevent.[41]

In some ways, the intravenous infusion of lidocaine is akin to regional analgesia. At doses in the order of 1.5 $mg \cdot kg^{-1} \cdot hr^{-1}$, this drug has robust support as an effective perioperative adjunct for the reduction of acute postoperative pain, particularly in visceral surgery.[42] More recently, a single well-conducted RCT showed impressive reductions in CPSP following breast cancer surgery when lidocaine was administered.[43] Given that lidocaine is an inexpensive and time-tested drug which is intimately familiar to all anesthesia providers, this exciting finding should certainly, at the very least, encourage us to study its effect on CPSP in other surgical models.

There is evidence that administration of gabapentin prior to surgery decreases both acute postoperative pain intensity and CPSP.[44] A single dose of 1,200 mg one hour before surgery is one example of the many different dosing regimens that have been tested in a variety of surgical models by randomized trials. In a recent meta-analysis, the pooled effect of gabapentin was to reduce the odds ratio of CPSP to 0.52 compared with controls, a worthwhile goal by any standard.[44] Gabapentin is a safe time-tested agent in the ambulatory treatment of neuropathic pain,[45] but its administration by protocol to large numbers of surgical patients would necessitate additional postoperative monitoring for somnolence.[44] The published literature on the use of pregabalin for the prevention of CPSP would appear to have been compromised by significant publication bias, and therefore, it cannot be relied on for clinical guidance at this time.[46]

Beyond the regional anesthesia literature lies a particularly thought-provoking nugget of information. A sub-analysis from one centre in the multicentre Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA) trial showed a 50% decrease in CPSP when 70% nitrous oxide was incorporated into the general anesthesia regime for non-cardiac surgery lasting more than two hours.[47] This is biologically plausible because of its known effect on the *N*-methyl-D-aspartate (NMDA) receptor and had been noted in animal models.[48] In the ENIGMA trial, the use of this agent for more than two hours was found to be associated with an increased risk of myocardial infarction,[49] and it is currently the subject of another multicentre study concerning its safety. Nevertheless, the practitioner with nitrous oxide in his or her repertoire might be tempted to use it when the risks of CPSP are especially high.

A collection of drugs that is commonly used in anesthetic practice comes next. They ought to have some effect on central sensitization based on their known actions, but unfortunately, there is a lack of evidence supporting their use as CPSP preventive agents. Ketamine's effect at the NMDA receptor makes it a good theoretical candidate for a CPSP preventive agent, and it is known to be effective against acute pain.[50] Nevertheless, neither of the two most recent studies of ketamine in thoracotomy shows that its administration made any difference to CPSP.[51,52] The situation for the alpha 2 adrenoceptor agonists, clonidine and dexmedetomidine, is subtly different. They reduce acute pain and perioperative morphine consumption, but none of the perioperative trials of these agents reported CPSP outcomes, so the question of their applicability in this regard is completely open.[53]

Finally, there is the fascinating question of the effect of remifentanil on CPSP. Unlike other interventions studied in the literature, the prevailing question is not whether it reduces acute pain or CPSP but whether it increases them, presumably by causing opioid-induced hyperalgesia, inducing rapid tolerance at the mu opioid receptor, or both. In 2005, high-dose intraoperative remifentanil was found to cause hyperalgesia and allodynia (two cutaneous signs of central hypersensitivity) in the acute phase in a human abdominal surgical model.[54] This led to a comparative study in thoracotomy of low- *vs* high-dose remifentanil, which duly found a higher risk of CPSP in the high-dose group.[55] Then again, the low-dose group received epidural analgesia throughout the procedure, while the high-dose group received it only following the procedure, which, in our view, denudes the certainty of that finding. Thereafter, a 90-subject data set of cardiac surgery subjects was subjected to retrospective logistic regression and was found to contain a very strong statistical association between the intraoperative use of remifentanil and CPSP.[56] These waters were muddied earlier in 2012, however, by results of another large RCT: A group receiving propofol/remifentanil maintenance for their thoracotomies was found to have a *lower*, not higher, risk of CPSP than a group receiving sevoflurane, with both groups receiving the same type of epidural coverage.[57] These confusing trials would be helped by a simple comparison of remifentanil *vs* another intraoperative opioid in which everything else is held constant and CPSP is measured. Until such a comparison is forthcoming, it seems that the literature cannot provide good guidance as to whether or not to avoid remifentanil in order to reduce the risk of CPSP. Nevertheless, given that the preoperative use of fentanyl for pain control before amputation was associated with a decreased risk of CPSP,[25] a case could be made for regarding remifentanil as guilty until proven innocent, since there are alternatives available that do more or less the same job in skilled hands. This is an argument that true remifentanil enthusiasts will find easy to resist.

Clearly, from both the research and clinical points of view, there is still much to be done in the quest to minimize CPSP.

On the research side, much could be achieved at low cost by simply performing late follow-up studies on

subjects who have already participated in RCTs of perioperative analgesia interventions. If the enthusiasm and resources for detailed sensory testing are unavailable, the detection of CPSP can be as simple a matter as a telephone call or a mailed questionnaire. Researchers who design future acute pain trials could greatly multiply the acquired knowledge by simply adding a component to measure CPSP. For designers of new CPSP trials, there are substantial and sensible (i.e., Canadian) guidelines that suggest a set of valid and reliable outcome measures for all important outcome domains.[58] Meta-analysts would rejoice if these were universally adopted. We have good cognizance of those patients who are at greatest risk of CPSP, but data are lacking on the effect of therapeutic measures to modify risks, such as preoperative fear, stress, and catastrophizing. This issue is just one of many potentially fruitful areas of study.

For the immediate future, clinicians will continue to operate in somewhat of an information vacuum when it comes to preventing CPSP. Nevertheless, a few things that would make an immediate difference to CPSP rates, if they were widely implemented, can be suggested to anesthesia providers with reasonable confidence (Table 2).

The earliest practitioners of anesthesia prayed only for their patients to survive. Subsequent generations took survival for granted and incrementally focused on eliminating as many adverse effects as possible from the immediate perioperative period. We are now at the threshold of an era in which our actions have a direct influence on issues that would have been unthinkable to our professional forefathers, such as wound healing and cancer recurrence.[59] Chronic post-surgical pain is such an issue. For far too many people, CPSP becomes a highly unwelcome yet permanent souvenir of their surgical journey. The task of reducing this reminder is eminently deserving of our individual and collective attention.

Table 2 Evidence-based strategies for anesthesia providers to reduce risk of chronic post-surgical pain (CPSP)

1. Screen preoperatively for anxiety, depression, and stress, and earmark those patients for special attention, especially if they are having a high-risk procedure.
2. Control preoperative pain aggressively.
3. Consider the perioperative use of gabapentin.
4. Use epidural analgesia for thoracotomy and major laparotomy and paravertebral blockade for breast surgery, and apply local anesthetic by single shot or local infusion whenever feasible.
5. If regional anesthesia or local infiltration of local anesthetic is not practical, consider perioperative intravenous lidocaine infusion.
6. Control immediate postoperative pain aggressively and for as long as necessary by any appropriate means. Encourage subsequent caregivers to do the same.

Key points

- On average, one in five persons undergoing surgery will develop chronic post-surgical pain (CPSP).
- Risk factors for CPSP include the type of surgery as well as characteristics of the patient.
- Most, but not all CPSP is attributable to nerve injury.
- Specific types of CPSP can be reduced by certain regional anesthetic techniques.
- Gabapentin is the only systemic drug for reducing CPSP that is currently supported by the highest grade of evidence.

Conflicts of interest None declared.

References

1. *Landmark T*, *Romundstad P*, *Dale O*, *Borchgrevink PC*, *Kaasa S*. Estimating the prevalence of chronic pain: validation of recall against longitudinal reporting (the HUNT pain study). Pain 2012; 153: 1368-73.
2. *Choiniere M*, *Dion D*, *Peng P*, *et al*. The Canadian STOP-PAIN project – Part 1: Who are the patients on the waitlists of multidisciplinary pain treatment facilities? Can J Anesth 2010; 57: 539-48.
3. *Shipton EA*. The transition from acute to chronic post surgical pain. Anaesth Intensive Care 2011; 39: 824-36.
4. *Haroutiunian S*, *Nikolajsen L*, *Finnerup NB*, *Jensen TS*. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain 2013; 154: 95-102.
5. *Geerts WH*, *Pineo GF*, *Heit JA*, *et al*. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3 Suppl): 338S-400S.
6. *Leaper DJ*. Risk factors for and epidemiology of surgical site infections. Surg Infect (Larchmt) 2010; 11: 283-7.
7. *Waitzkin H*. Doctor-patient communication. Clinical implications of social scientific research. JAMA 1984; 252: 2441-6.
8. *Johansen A*, *Romundstad L*, *Nielsen CS*, *Schirmer H*, *Stubhaug A*. Persistent postsurgical pain in a general population: prevalence and predictors in the Tromso study. Pain 2012; 153: 1390-6.
9. *Crombie IK*, *Davies HT*, *Macrae WA*. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain 1998; 76: 167-71.
10. *Katz J*, *Seltzer Z*. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother 2009; 9: 723-44.
11. *Kehlet H*, *Jensen TS*, *Woolf CJ*. Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367: 1618-25.
12. *Cousins MJ*, *Mather LE*. Intrathecal and epidural administration of opioids. Anesthesiology 1984; 61: 276-310.
13. *Seebach CL*, *Kirkhart M*, *Lating JM*, *et al*. Examining the role of positive and negative affect in recovery from spine surgery. Pain 2012; 153: 518-25.
14. *VanDenKerkhof EG*, *Hopman WM*, *Reitsma ML*, *et al*. Chronic pain, healthcare utilization, and quality of life following gastrointestinal surgery. Can J Anesth 2012; 59: 670-80.
15. *Franneby U*, *Sandblom G*, *Nordin P*, *Nyren O*, *Gunnarsson U*. Risk factors for long-term pain after hernia surgery. Ann Surg 2006; 244: 212-9.

16. *Liu SS*, *Buvanendran A*, *Rathmell JP*, *et al*. A cross-sectional survey on prevalence and risk factors for persistent postsurgical pain 1 year after total hip and knee replacement. Reg Anesth Pain Med 2012; 37: 415-22.
17. *Dworkin RH*, *McDermott MP*, *Raja SN*. Preventing chronic postsurgical pain: how much of a difference makes a difference? Anesthesiology 2010; 112: 516-8.
18. *von Sperling ML*, *Hoimyr H*, *Finnerup K*, *Jensen TS*, *Finnerup NB*. Persistent pain and sensory changes following cosmetic breast augmentation. Eur J Pain 2011; 15: 328-32.
19. *Tandon S*, *Sabanegh E Jr*. Chronic pain after vasectomy: a diagnostic and treatment dilemma. BJU Int 2008; 102: 166-9.
20. *Janssen KJ*, *Kalkman CJ*, *Grobbee DE*, *Bonsel GJ*, *Moons KG*, *Vergouwe Y*. The risk of severe postoperative pain: modification and validation of a clinical prediction rule. Anesth Analg 2008; 107: 1330-9.
21. *Althaus A*, *Hinrichs-Rocker A*, *Chapman R*, *et al*. Development of a risk index for the prediction of chronic post-surgical pain. Eur J Pain 2012; 16: 901-10.
22. *Hinrichs-Rocker A*, *Schulz K*, *Jarvinen I*, *Lefering R*, *Simanski C*, *Neugebauer EA*. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) – a systematic review. Eur J Pain 2009; 13: 719-30.
23. *Kristensen AD*, *Ahlburg , Lauridsen MC*, *Jensen TS*, *Nikolajsen L*. Chronic pain after inguinal hernia repair in children. Br J Anaesth 2012; 109: 603-8.
24. *Katz J*, *Clarke H*, *Seltzer Z*. Preventive analgesia: quo vadimus? Anesth Analg 2011; 113: 1242-53.
25. *Karanikolas M*, *Aretha D*, *Tsolakis I*, *et al*. Optimized perioperative analgesia reduces chronic phantom limb pain intensity, prevalence, and frequency: a prospective, randomized, clinical trial. Anesthesiology 2011; 114: 1144-54.
26. *Rathmell JP*, *Kehlet H*. Do we have the tools to prevent phantom limb pain? Anesthesiology 2011; 114: 1021-4.
27. *Tasmuth T*, *Blomqvist C*, *Kalso E*. Chronic post-treatment symptoms in patients with breast cancer operated in different surgical units. Eur J Surg Oncol 1999; 25: 38-43.
28. *Liem MS*, *van Duyn EB*, *van der Graaf Y*, *van Vroonhoven TJ*, *Coala Trial Group*. Recurrences after conventional anterior and laparoscopic inguinal hernia repair: a randomized comparison. Ann Surg 2003; 237: 136-41.
29. *Kalso E*, *Mennander S*, *Tasmuth T*, *Nilsson E*. Chronic post-sternotomy pain. Acta Anaesthesiol Scand 2001; 45: 935-9.
30. *Alfieri S*, *Amid PK*, *Campanelli G*, *et al*. International guidelines for prevention and management of post-operative chronic pain following inguinal hernia surgery. Hernia 2011; 15: 239-49.
31. *Bischoff JM*, *Aasvang EK*, *Kehlet H*, *Werner MU*. Does nerve identification during open inguinal herniorrhaphy reduce the risk of nerve damage and persistent pain? Hernia 2012; 16: 573-7.
32. *Andreae MH, Andreae DA*. Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery. Cochrane Database Syst Rev 2012; 10: CD007105.
33. *Senturk M*, *Ozcan PE*, *Talu GK*, *et al*. The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesth Analg 2002; 94: 11-5.
34. *Lavand'homme P, De Kock M, Waterloos H*. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. Anesthesiology 2005; 103: 813-20.
35. *Kairaluoma PM*, *Bachmann MS*, *Rosenberg PH*, *Pere PJ*. Preincisional paravertebral block reduces the prevalence of chronic pain after breast surgery. Anesth Analg 2006; 103: 703-8.
36. *Mounir K*, *Bensghir M*, *Elmoqaddem A*, *et al*. Efficiency of bupivacaine wound subfasciale infiltration in reduction of postoperative pain after inguinal hernia surgery (French). Ann Fr Anesth Reanim 2010; 29: 274-8.
37. *Paxton LD*, *Huss BK*, *Loughlin V*, *Mirakhur RK*. Intra-vas deferens bupivacaine for prevention of acute pain and chronic discomfort after vasectomy. Br J Anaesth 1995; 74: 612-3.
38. *Singh K, Phillips FM, Kuo E, Campbell M*. A prospective, randomized, double-blind study of the efficacy of postoperative continuous local anesthetic infusion at the iliac crest bone graft site after posterior spinal arthrodesis: a minimum of 4-year follow-up. Spine (Phila Pa 1976) 2007; 32: 2790-6.
39. *Shahin AY*, *Osman AM*. Intraperitoneal lidocaine instillation and postcesarean pain after parietal peritoneal closure: a randomized double blind placebo-controlled trial. Clin J Pain 2010; 26: 121-7.
40. *Richman JM*, *Liu SS*, *Courpas G*, *et al*. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesth Analg 2006; 102: 248-57.
41. *Pitkanen MT*, *Aromaa U*, *Cozanitis DA*, *Forster JG*. Serious complications associated with spinal and epidural anaesthesia in Finland from 2000 to 2009. Acta Anaesthesiol Scand 2013; 57: 553-64.
42. *Vigneault L*, *Turgeon AF*, *Cote D*, *et al*. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anesth 2011; 58: 22-37.
43. *Grigoras A*, *Lee P*, *Sattar F*, *Shorten G*. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. Clin J Pain 2012; 28: 567-72.
44. *Clarke H*, *Bonin RP*, *Orser BA*, *Englesakis M*, *Wijeysundera DN*, *Katz J*. The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. Anesth Analg 2012; 115: 428-42.
45. *Finnerup NB*, *Otto M*, *McQuay HJ*, *Jensen TS*, *Sindrup SH*. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118: 289-305.
46. *Chelly JE*. Pregabalin effective for the prevention of chronic postsurgical pain: really? Anesth Analg 2013; 116: 507-8.
47. *Chan MT*, *Wan AC*, *Gin T*, *Leslie K*, *Myles PS*. Chronic postsurgical pain after nitrous oxide anesthesia. Pain 2011; 152: 2514-20.
48. *Richebe P*, *Rivat C*, *Creton C*, *et al*. Nitrous oxide revisited: evidence for potent antihyperalgesic properties. Anesthesiology 2005; 103: 845-54.
49. *Leslie K*, *Myles PS*, *Chan MT*, *et al*. Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. Anesth Analg 2011; 112: 387-93.
50. *Laskowski K*, *Stirling A*, *McKay WP*, *Lim HJ*. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anesth 2011; 58: 911-23.
51. *Joseph C*, *Gaillat F*, *Duponq R*, *et al*. Is there any benefit to adding intravenous ketamine to patient-controlled epidural analgesia after thoracic surgery? A randomized double-blind study. Eur J Cardiothorac Surg 2012; 42: e58-65.
52. *Mendola C*, *Cammarota G*, *Netto R*, *et al*. S+-ketamine for control of perioperative pain and prevention of post thoracotomy pain syndrome: a randomized, double-blind study. Minerva Anestesiol 2012; 78: 757-66.
53. *Blaudszun G*, *Lysakowski C*, *Elia N*, *Tramer MR*. Effect of perioperative systemic alpha 2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2012; 116: 1312-22.
54. *Joly V*, *Richebe P*, *Guignard B*, *et al*. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology 2005; 103: 147-55.
55. *Salengros JC*, *Huybrechts I*, *Ducart A*, *et al*. Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. J Cardiothorac Vasc Anesth 2010; 24: 608-16.

56. *van Gulik L*, *Ahlers SJ*, *van de Garde EM*, *et al*. Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. Br J Anaesth 2012; 109: 616-22.
57. *Song JG*, *Shin JW*, *Lee EH*, *et al*. Incidence of post-thoracotomy pain: a comparison between total intravenous anaesthesia and inhalation anaesthesia. Eur J Cardiothorac Surg 2012; 41: 1078-82.
58. *VanDenKerkhof EG*, *Peters ML*, *Bruce J*. Chronic pain after surgery: time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies. Clin J Pain 2013; 29: 2-8.
59. *Kavanagh T*, *Buggy DJ*. Can anaesthetic technique effect postoperative outcome? Curr Opin Anaesthesiol 2012; 25: 185-98.