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Factors Contributing to Pain Chronicity

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Abstract

The chronicity of pain is the feature of pain that is least understood and most directly linked with our inability to effectively manage pain. Acute pain is relatively responsive to our current pharmacologic and interventional armamentarium. However, as pain persists, our ability to treat effectively diminishes and the patient's frustration and resource utilization increases. This article explores our current understanding of the factors linked to pain duration and the transition from acute to chronic pain in both human and animal models, and across a spectrum of human chronic pain conditions.

Introduction

Advances in pain research have elucidated a great deal about the factors that may lead to chronic pain. Peripheral injury leads to increased excitability in peripheral nociceptors (peripheral sensitization) that manifests as primary hyperalgesia. Subsequent barrage of the central nervous system (CNS) leads to increased and prolonged excitability of CNS nociceptors (central sensitization), leading to increased sensitivity to painful stimuli in areas of normal tissue removed from the site of injury (secondary hyperalgesia). Furthermore, peripheral nerve injury is accompanied by a variety of changes, including the new expression of sodium channels, adrenergic receptors, and cholinergic receptors that contribute to depolarization of injured nociceptors. This depolarization of injured nociceptors can result in adequate sodium and calcium flux to endow the injured nociceptor with a pacemaker function in which the cell reaches action potentials spontaneously and regularly without outside stimulation. All of these elements make the occurrence of chronic pain following injury (especially nerve injury) seem rather predictable. However, these factors do not explain why most people have no persistent pain following injury (or even nerve injury).

Every surgery cuts cutaneous nerves. It is well documented that even these small cutaneous nerves can lead to chronic neuropathic pain (scar neuromas). However, most patients do not experience persistent pain following surgery. Similarly, many patients continue to show evidence of nerve damage following acute herpes zoster but most do not progress to the chronically painful state of postherpetic neuralgia. The mystery is not why some develop chronic pain in the face of this biology but rather why most do not.

A great many studies have focused on predictors and causes of pain severity, pain thresholds, treatments for reducing acute and chronic pain severity, and even incidence. However, the number of studies specifically studying the duration of pain across the spectrum from acute to chronic pain has been limited. As a result, our understanding of the specific variables influencing pain duration has been poorly elucidated. The factors controlling the duration of pain following an injury are highly important because chronic pain may be nothing more than the extended duration of acute pain. In other words, the same factors that lead to delayed pain

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resolution following injury may also lead to unresolving pain when carried to the extreme. Alternatively, chronic pain may arise from fundamentally different biology and factors than those leading to delayed pain resolution. This article highlights animal and human research explicitly examining pain duration and the shift from acute to chronic pain.

Animal Data

Animal studies suggest a crucial role for the CNS in general and the brain in particular in determining the persistence of pain. Rat data suggest that the duration of pain is controlled by supraspinal systems projecting from the rostral ventromedial medulla (RVM) of the brain to the spinal cord [1,2]. Our understanding of these descending projections has evolved to encompass the presence of “on” cells that functionally facilitate the transmission of pain in the dorsal horn of the spinal cord. Colocalized with these “on” cells are “off” cells that project to similar locations but have the opposite effect—inhibiting pain transmission at the first synapse in the dorsal horn of the spinal cord. Within this context, the perception of pain or its extinguishment can be understood as specifically under control of supraspinal CNS systems that may be more determinant in the persistence of pain following injury than the nature of the peripheral nerve injury. Furthermore, the experience of pain can be conceived as an active supraspinally modulated behavior rather than a passive sensory experience.

The relative importance of these supraspinal systems in the RVM and the nature of the peripheral injury in determining the duration of pain and its eventual perpetuation or cessation is illustrated by a series of elegant experiments in the rat. Selective block, physical lesion, or immunologic reduction of opioid receptor–positive “on” cells of the rat RVM creates a rat in which nerve injury pain can be initiated but not maintained [3–6]. In other words, injuries that reliably produce chronic pain in intact rats produce acute, but not chronic, pain in the absence of descending signals from the brain. These findings suggest that the lesions in the RVM do not create analgesia per se, but rather regulate the duration of pain and its transition from acute to chronic. These signals appear to be dependent at least in part on central cholecystokinin release, and are elicited by the presence of the peripheral nerve injury.

Other studies point to the importance of microglial activation in the CNS in perpetuating acute pain. Intrathecal minocycline (a known microglial inhibitor), but not saline control, has been shown to prevent the development of persistent mechanical allodynia and thermal hyperalgesia induced by spinal nerve ligation [7•]. Minocycline also inhibits the generation of persistent mechanical allodynia in both acute and persistent pain models induced by sciatic nerve inflammation (sciatic inflammatory neuropathy [SIN]). Moreover, minocycline was able to attenuate established SIN-induced allodynia 1 day but not 1 week after sciatic nerve injury [8]. These findings suggest an early and crucial role for microglial cells in initiating, but not necessarily maintaining, enhanced pain responses. Furthermore, similar to the role of the RVM, early reactive changes in microglial activation in the CNS appear to be more determinant than the mode or severity of injury in determining the persistence of pain following nerve injury. Together, these animal experiments suggest that a significant part of the variance in whether an acute injury will cause prolonged pain is likely determined by activity in the CNS rather than in the peripheral nervous system or the mode of injury.

Human Data

In humans, fear in particular appears to play a central role in the duration of pain. Catastrophizing thoughts lead to pain-related fear [9,10], and in prospective longitudinal studies, catastrophizing and fear have been specifically associated with an increased risk of chronic back pain 1 year after acute low back injury [11,12•]. Catastrophizing was more than 7 times more powerful a predictor than any other predictor or clinical variable among acute

back pain patients in determining the risk of subsequent chronic pain [11]. These findings are bolstered by the findings of a prospective population-based study linking fear in pain-free individuals with the risk of subsequently developing chronic pain complaints [13]. Pain-related fear causes patients with pain to overpredict the severity of pain they will experience. This results in subsequent overproduction of avoidance behavior, which conceptually may delay pain resolution [14]. Fear and anxiety may exert pain-modulating effects through brain activity in the medial prefrontal region, ventral lateral frontal region, and cingulate regions associated with monitoring and evaluation of affective responses [15]. Links between these regions and the RVM remain to be demonstrated.

Anxiety and depression may also be markers for CNS physiology that play a significant role in the durability of pain. Between 30% and 65% of patients with chronic pain have comorbid depression [16]. Longitudinal epidemiologic studies evaluating depression and anxiety together [17,18] or depression alone [19–23] indicate that patients with depression and anxiety are between 2 to 5 times more likely to have a new chronic pain problem at follow-up from 1 to 8 years later. This occurs despite the robust findings reviewed and expanded on by Dworkin et al. [24] that patients with depression appear to be *less* sensitive to pain in response to experimental noxious stimuli compared with healthy controls. These studies suggest that depression and possibly anxiety may exert elevated risk of chronic pain by either altering pain durability or altering new pain incidence rather than by altering pain thresholds or pain severity. Together, these findings argue for future emphasis on studying pain duration rather than pain severity or pain thresholds.

There remains a great need to define if the elevated prevalence seen at follow-up among those with elevated baseline fear, anxiety, and depression are related to increased onset of new pain complaints or decreased resolution (ie, increased duration) of new pain complaints. Furthermore, there is a need to characterize the mechanisms by which these psychological factors either increase the risk of new pain complaints or lengthen the duration of these new pain complaints. It is tempting to speculate, based on the animal data previously cited, that the supraspinal physiology manifesting as fear, anxiety, or depression may be a marker of global CNS processes that simultaneously modulate either descending signals from the RVM or mark elevated levels of microglial activation in response to injury, thereby enhancing both pain duration and the probability that new injuries will result in chronic pain.

The Postsurgical Model

The occurrence of chronic postsurgical pain has provided an opportunity to examine the predictive nature of psychologic distress on the subsequent occurrence of chronic pain. Unlike the epidemiologic studies previously described, postsurgical studies look among a group in whom all have an injury. In other words, there is equal incidence in the cohort of a new acute pain condition. Therefore, elevated levels of persistent pain and the factors predicting persistent postsurgical pain more directly implicate these psychologic factors in affecting pain resolution and duration (rather than incidence rates).

State-Trait Anxiety Index and Beck Depression Inventory scores have been reported to be significantly correlated with pain 12 months after knee surgery [25]. Preoperative pain was also found to be a significant long-term predictor of chronic postsurgical knee pain [26].

Following thoracotomy, greater continuous pain in the acute postoperative setting was also significantly correlated with chronic postoperative pain [27]. Advanced age has been found to predict greater duration of residual post-thoracotomy pain in some studies [28], but reduced risk in other studies [27]. The role of gender has been similarly uncertain. The female gender has been found to predict increased risk for prolonged pain by a study in a Japanese cohort of 85 patients [29] and a study of 120 patients [30]. However, another study of 149 post-

thoracotomy patients failed to show a significant correlation [27]. It has been proposed that women experience greater sensitivity to pain, with some work suggesting a neurophysiologic basis in the brain for gender differences [31]. It is imperative, however, that cultural effects are investigated instead of ignored. In stark contrast with these studies of Japanese and Brazilian women, a study of more than 2000 patients in China found that women experienced less pain and used fewer analgesics [32]. Although many studies have documented the risks associated with the occurrence of chronic postsurgical pain, to our knowledge only one small study has specifically measured pain duration following surgery [33]. Unfortunately, notwithstanding undergoing a thoracotomy, patients in this study received no opioids, limiting the generalizability to the more common experience seen in hospitals where practically all postoperative patients receive opioids. Nonetheless, the study concluded that anxiety and aggressivity were correlated with prolonged postsurgical pain.

Psychophysical Approaches

Quantitative sensory testing (QST) has yielded varying results when used to quantify peripheral and CNS function that may predict persistent pain. One study comparing 46 patients reporting moderate to severe postherniorrhaphy pain 1 year following surgery was compared with a control group of pain-free postherniorrhaphy patients. Overall, the significant peripheral sensory dysfunction found was hypoesthesia to various sensory modalities when comparing pain with pain-free patients. Equally robust, however, was the evidence of CNS functional change manifested in patients with persistent pain as a higher incidence and intensity of temporal summation to repetitive pinprick stimulation around the scar compared with the contralateral side. In contrast, temporal summation was absent in the pain-free controls. Other QST changes, such as warmth detection thresholds, were abnormal in both those with and without chronic pain [34]. In a similar study of 72 patients 6 to 12 months after open herniorrhaphy, QST showed that mechanical hypoesthesia and tactile allodynia were common findings in the surgical area. However, these sensory disturbances did not occur more often in patients with pain than those without pain. Also, no difference was observed in thermal detection thresholds and heat pain thresholds between pain and nonpain patients [35]. The study concluded that QST had a low specificity for chronic pain after inguinal herniorrhaphy. These results highlight the common occurrence of sustained peripheral nervous system dysfunction following surgery as well as the unclear relationship that this dysfunction has with pain duration and the incidence of chronic pain. In contrast, peripherally manifested signs of altered CNS function, such as temporal summation, may have better predictive value.

The role that opioids play in pain duration following surgery specifically or acute injury in general has received little attention. Many animal studies have documented that opioids generate a state of pain hypersensitivity to noxious mechanical, chemical, and thermal stimuli termed opioid-induced hyperalgesia (OIH). OIH may arise rapidly in humans in both the experimental [36] and perioperative setting [37]. However, the role of this hyperalgesia in the persistence of pain over time is uncertain. Recently, Webster et al. [38•] demonstrated a dose-response relationship between the early use of prescription opioids for acute low back pain and both increased pain duration and elevated risk of chronic opioid use. However, this intriguing finding may simply reflect that early use of opioids is a marker of disease severity. There is a great need to examine how pain affects opioid use duration and conversely how opioids affect pain resolution rates. The work cited above suggests that opioid use may exert a prolonging effect on the duration of pain even when controlled for pain severity.

Only a handful of human studies in other areas have longitudinally studied the factors related to pain duration and directly measured the rate of pain resolution. These studies have used the model of acute herpes zoster (AHZ) and have been largely focused on the specific use of antiviral medications to speed pain resolution. Models of acute to chronic pain persistence,

including AHZ and acute back pain, have proven to be intrinsically limited by the fact that patients already have pain when they become available for study, and such patients are only sporadically available to study. However, one intriguing finding from these studies is that factors associated with increased rates of pain resolution in AHZ (initial pain severity, younger age, use of antiviral medication, and use of continuous local anesthetic epidural blockade) [39–44] have also been associated with reduced prevalence of chronic pain (postherpetic neuralgia) in other studies [45–47]. Within this context, the rate of pain resolution may be both a clinically important end point in itself and an equally important early measurable indicator of the risk of chronic pain across a wide range of acute injuries. There is a significant need to further assess in other models if factors that influence the rate of pain resolution produce corresponding changes in the rate of chronic postsurgical pain.

Conclusions

Important studies have identified intrathecal clonidine [48], intraoperative ketamine [49], and epidural analgesia [50] as modalities that may reduce the likelihood of chronic postsurgical pain. However, these studies have not investigated the link between this long-term outcome for a minority of patients with their effects of pain duration more generally among all comers. In other words, is the reduction in chronic pain seen with these agents a manifestation of altering the physiology that controls pain duration more generally? Future work should explore the link between reductions in pain duration and the incidence of chronic pain in postsurgical patients. Finally, there is a tremendous gap in the literature on postsurgical pain duration, with a great need for studies to test whether we can intervene therapeutically to reduce the duration of acute and subacute pain for the 34 million Americans undergoing surgery every year. The perioperative setting provides a robust research environment to carefully characterize variables that may confer risk of delayed pain resolution before the first onset of pain, in a setting that reliably produces a steady stream of subjects of all ages, races, and genders. Furthermore, the perioperative setting is an ideal setting for future interventions aimed at prophylaxis or early intervention for those at greatest risk of reduced pain resolution. This model should be useful to investigators interested in pain duration and the crucial transition from acute to chronic pain.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Pan ZZ, Williams JT, Osborne PB. Opioid actions on single nucleus raphe magnus neurons from rat and guinea-pig in vitro. *J Physiol* 1990;427:519–532. [PubMed: 1976803]
2. Heinricher MM, Morgan MM, Tortorici V, Fields HL. Disinhibition of off-cells and antinociception produced by an opioid action within the rostral ventromedial medulla. *Neuroscience* 1994;63:279–288. [PubMed: 7898652]
3. Pertovaara A, Wei H, Hämäläinen MM. Lidocaine in the rostroventromedial medulla and the periaqueductal gray attenuates allodynia in neuropathic rats. *Neurosci Lett* 1996;218:127–130. [PubMed: 8945744]
4. Kovelowski CJ, Ossipov MH, Sun H, et al. Supraspinal cholecystokinin may drive tonic descending facilitation mechanisms to maintain neuropathic pain in the rat. *Pain* 2000;87:265–273. [PubMed: 10963906]
5. Ossipov MH, Hong Sun T, Malan P, et al. Mediation of spinal nerve injury induced tactile allodynia by descending facilitatory pathways in the dorsolateral funiculus in rats. *Neurosci Lett* 2000;290:129–132. [PubMed: 10936694]

6. Porreca F, Burgess SE, Gardell LR, et al. Inhibition of neuropathic pain by selective ablation of brainstem medullary cells expressing the mu-opioid receptor. *J Neurosci* 2001;21:5281–5288. [PubMed: 11438603]
7. Lin CS, Tsaur ML, Chen CC, et al. Chronic intrathecal infusion of minocycline prevents the development of spinal-nerve ligation-induced pain in rats. *Reg Anesth Pain Med* 2007;32:209–216. [PubMed: 17543815] Explores the possible role that microglial activation plays in the perpetuation of pain and the possible modulating effect of minocycline.
8. Ledeboer A, Sloane EM, Milligan ED, et al. Minocycline attenuates mechanical allodynia and proinflammatory cytokine expression in rat models of pain facilitation. *Pain* 2005;115:71–83. [PubMed: 15836971]
9. McCracken LM, Gross RT. Does anxiety affect coping with chronic pain? *Clin J Pain* 1993;9:253–259. [PubMed: 8118089]
10. Vlaeyen JW, Kole-Snijders AM, Boeren RG, van Eek H. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain* 1995;62:363–372. [PubMed: 8657437]
11. Burton AK, Tillotson KM, Main CJ, Hollis S. Psychosocial predictors of outcome in acute and subchronic low back trouble. *Spine* 1995;20:722–728. [PubMed: 7604349]
12. Swinkels-Meewisse IE, Roelofs J, Schouten EG, et al. Fear of movement/(re)injury predicting chronic disabling low back pain: a prospective inception cohort study. *Spine* 2006;31:658–664. [PubMed: 16540870] A study defining the crucial role of fear in transitioning from acute to chronic pain.
13. Severeijns R, Vlaeyen JW, van den Hout MA, Picavet HS. Pain catastrophizing and consequences of musculoskeletal pain: a prospective study in the Dutch community. *J Pain* 2005;6:125–132. [PubMed: 15694879]
14. McCracken LM, Gross RT, Sorg PJ, Edmands TA. Prediction of pain in patients with chronic low back pain: effects of inaccurate prediction and pain-related anxiety. *Behav Res Ther* 1993;31:647–652. [PubMed: 8216166]
15. Ochsner KN, Ludlow DH, Knierim K, et al. Neural correlates of individual differences in pain-related fear and anxiety. *Pain* 2006;120:69–77. [PubMed: 16364548]
16. Katona C, Peveler R, Dowrick C, et al. Pain symptoms in depression: definition and clinical significance. *Clin Med* 2005;5:390–395. [PubMed: 16138496]
17. Croft PR, Papageorgiou AC, Ferry S, et al. Psychologic distress and low back pain. Evidence from a prospective study in the general population. *Spine* 1995;20:2731–2737. [PubMed: 8747252]
18. Hotopf M, Mayou R, Wadsworth M, Wessely S. Temporal relationships between physical symptoms and psychiatric disorder. Results from a national birth cohort. *Br J Psychiatry* 1998;173:255–261. [PubMed: 9926103]
19. Currie SR, Wang J. More data on major depression as an antecedent risk factor for first onset of chronic back pain. *Psychol Med* 2005;35:1275–1282. [PubMed: 16168150]
20. Larson SL, Clark MR, Eaton WW. Depressive disorder as a long-term antecedent risk factor for incident back pain: a 13-year follow-up study from the Baltimore Epidemiological Catchment Area sample. *Psychol Med* 2004;34:211–219. [PubMed: 14982127]
21. Carroll LJ, Cassidy JD, Côté P. Depression as a risk factor for onset of an episode of troublesome neck and low back pain. *Pain* 2004;107:134–139. [PubMed: 14715399]
22. Von Korff M, Le Resche L, Dworkin SF. First onset of common pain symptoms: a prospective study of depression as a risk factor. *Pain* 1993;55:251–258. [PubMed: 8309712]
23. Magni G, Moreschi C, Rigatti-Luchini S, Merskey H. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. *Pain* 1994;56:289–297. [PubMed: 8022622]
24. Dworkin RH, Clark WC, Lipsitz JD. Pain responsivity in major depression and bipolar disorder. *Psychiatry Res* 1995;56:173–181. [PubMed: 7667442]
25. Brander VA, Stulberg SD, Adams AD, et al. Predicting total knee replacement pain: a prospective, observational study. *Clin Orthop Relat Res* 2003;416:27–36. [PubMed: 14646737]
26. Haythornthwaite JA, Raja SN, Fisher B, et al. Pain and quality of life following radical retropubic prostatectomy. *J Urol* 1998;160:1761. [PubMed: 9783947]
27. Pluijms WA, Steegers MAH, Verhagen AFTM, et al. Chronic post-thoracotomy pain: a retrospective study. *Acta Anaesthesiol Scand* 2006;50:804–808. [PubMed: 16879462]

28. Matsunaga M, Dan K, Manable FY, et al. Residual pain of 90 thoracotomy patients with malignancy and non-malignancy. *Pain* 1990;5(Suppl):S148.
29. Gotoda Y, Kambara N, Sakai T, et al. The morbidity, time course and predictive factors for persistent post-thoracotomy pain. *Eur J Pain* 2001;5:89. [PubMed: 11394926]
30. Ochroch EA, Gottschalk A, Troxel AB, Farrar JT. Women suffer more short and long-term pain than men after major thoracotomy. *Clin J Pain* 2006;22:491. [PubMed: 16772805]
31. Paulson PE, Minoshima S, Morrow TJ, Casey KL. Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. *Pain* 1998;76:223. [PubMed: 9696477]
32. Chia YY, Chow LH, Hung CC, et al. Gender and pain upon movement are associated with the requirements for postoperative patient-controlled iv analgesia: a prospective survey of 2,298 Chinese patients. *Can J Anaesth* 2002;49:249. [PubMed: 11861342]
33. Bachiocco V, Morselli-Labate AM, Rusticali AG, et al. Intensity, latency and duration of post-thoracotomy pain: relationship to personality traits. *Funct Neurol* 1990;5:321–332. [PubMed: 2093050]
34. Aasvang EK, Brandsborg B, Christensen B, et al. Neurophysiological characterization of postherniotomy pain. *Pain* 2008;137:173–181. [PubMed: 17976914]
35. Mikkelsen T, Werner MU, Lassen B, Kehlet H. Pain and sensory dysfunction 6 to 12 months after inguinal herniotomy. *Anesth Analg* 2004;99:146–151. [PubMed: 15281521]
36. Angst MS, Koppert W, Pahl I, et al. Short-term infusion of the mu-opioid agonist remifentanyl in humans causes hyperalgesia during withdrawal. *Pain* 2003;106:49–57. [PubMed: 14581110]
37. Chia YY, Liu K, Wang JJ, et al. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. *Can J Anaesth* 1999;46:872–877. [PubMed: 10490157]
38. Webster BS, Verma SK, Gatchel RJ. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. *Spine* 2007;32:2127–2132. [PubMed: 17762815] A seminal article suggesting a contributory role of opioids in people transitioning from acute to chronic pain.
39. Whitley RJ, Shukla S, Crooks RJ. The identification of risk factors associated with persistent pain following herpes zoster. *J Infect Dis* 1998;178(Suppl 1):S71–S75. [PubMed: 9852979]
40. Huff JC, Drucker JL, Clemmer A, et al. Effect of oral acyclovir on pain resolution in herpes zoster: a reanalysis. *J Med Virol* 1993;93–96. [PubMed: 8245901]
41. Tyring S, Barbarash RA, Nahlik JE, et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. *Ann Intern Med* 1995;123:89–96. [PubMed: 7778840]
42. Tyring SK, Beutner KR, Tucker BA, et al. Antiviral therapy for herpes zoster: randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. *Arch Fam Med* 2000;9:863–869. [PubMed: 11031393]
43. Manabe H, Dan K, Higa K. Continuous epidural infusion of local anesthetics and shorter duration of acute zoster-associated pain. *Clin J Pain* 1995;11:220–228. [PubMed: 8535042]
44. Manabe H, Dan K, Hirata K, et al. Optimum pain relief with continuous epidural infusion of local anesthetics shortens the duration of zoster-associated pain. *Clin J Pain* 2004;20:302–308. [PubMed: 15322436]
45. Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. *Pain* 1996;67:241–251. [PubMed: 8951917]
46. Dworkin RH, Hartstein G, Rosner HL, et al. A high-risk method for studying psychosocial antecedents of chronic pain: the prospective investigation of herpes zoster. *J Abnorm Psychol* 1992;101:200–205. [PubMed: 1537967]
47. Pasqualucci A, Pasqualucci V, Galla F, et al. Prevention of post-herpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone. *Acta Anaesthesiol Scand* 2000;44:910–918. [PubMed: 10981565]
48. De Kock M, Lavand'homme P, Waterloos H. The short-lasting analgesia and long-term antihyperalgesic effect of intrathecal clonidine in patients undergoing colonic surgery. *Anesth Analg* 2005;101:566–572. [PubMed: 16037177]table of contents

49. 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;103:813–820. [PubMed: 16192774]
50. Senturk M, Ozcan PE, Talu GK, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* 2002;94:11–15. [PubMed: 11772793]table of contents