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Perioperative Interventions to Reduce Chronic Postsurgical Pain

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Abstract

Approximately 10% of patients following a variety of surgeries develop chronic postsurgical pain. Reducing chronic postoperative pain is especially important to reconstructive surgeons because common operations such as breast and limb reconstruction have even higher risk for developing chronic postsurgical pain. Animal studies of posttraumatic nerve injury pain demonstrate that there is a critical time frame before and immediately after nerve injury in which specific interventions can reduce the incidence and intensity of chronic neuropathic pain behaviors–so called "preventative analgesia." In animal models, perineural local anesthetic, systemic intravenous local anesthetic, perineural clonidine, systemic gabapentin, systemic tricyclic antidepressants, and minocycline have each been shown to reduce pain behaviors days to weeks after treatment. The translation of this work to humans also suggests that brief perioperative interventions may protect patients from developing new chronic postsurgical pain. Recent clinical trial data show that there is an opportunity during the perioperative period to dramatically reduce the incidence and severity of chronic postsurgical pain. The surgeon, working with the anesthesiologist, has the ability to modify both early and chronic postoperative pain by implementing an evidence-based preventative analgesia plan.

Keywords

pain; neuropathic pain; preventative analgesia

Chronic postoperative surgical pain presents a continuing clinical problem. Approximately 10% of patients following a variety of surgeries develop chronic postsurgical pain.[1] Recent clinical trial data show that there is an opportunity during the perioperative period to dramatically reduce the incidence and severity of chronic postsurgical pain. The fact that perioperative medical management can reduce chronic pain is of keen interest to surgeons, as every incision damages nerves and risks the development of chronic pain. Mitigating postoperative pain is especially important to reconstructive surgeons because common operations such as breast and limb reconstruction have increased risk for developing chronic

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postsurgical pain.[2–4] The surgeon, working with the anesthesiologist, has the ability to modify the early and chronic postoperative pain experience by implementing an evidence-based program that employs the concept of “preventative analgesia.”

Chronic pain following nerve injury has been extensively studied using animal models. These studies have found that there is a critical time frame before and immediately after nerve injury in which specific interventions can reduce the incidence and intensity of chronic neuropathic pain behaviors–so called “preventative analgesia.” In animal models, perineural local anesthetic,[5] systemic intravenous local anesthetic,[6] perineural clonidine,[7] systemic gabapentin,[8] systemic tricyclic antidepressants,[9] and minocycline[10,11] have each been shown to reduce pain behaviors days to weeks after treatment. The translation of this work to humans also suggests that brief perioperative interventions may protect patients from developing new chronic postsurgical pain.

The core issues for surgeons to understand regarding the occurrence of new chronic postsurgical pain are:

1. Chronic postsurgical pain is most often not a failure of surgical technique but a function of good biology gone bad.
2. Despite the truth of the first point, the surgeon has several efficacious interventions to reduce chronic postsurgical pain.
3. Perioperatively there is a critical window of time to intervene to reduce chronic postsurgical pain.
4. Preventing postsurgical chronic pain is the responsibility of the surgeon. It is the surgeon who sees the patient before surgery and who has the opportunity to initiate preoperative medications to reduce chronic postsurgical pain, and it is the surgeon who will initially manage the patient’s medications postoperatively.
5. One common thread has emerged in studies examining chronic postsurgical pain; severe pain immediately postop increases the risk of chronic pain. This may be mediated by the long-term sensitization of pain-carrying neurons by brief periods of high-intensity pain.

The remainder of this paper will provide information on their effectiveness at reducing postsurgical chronic pain in humans (▶Table 1).

Gabapentinoids

Gabapentinoids (gabapentin and pregabalin) are anticonvulsant medications that may reduce acute and chronic pain after surgery.[2] Both drugs bind to a subunit of voltagegated calcium channels thought to participate in evoked neurotransmitter release in pain-carrying neurons. In addition, these drugs may also increase spinal descending inhibitory noradrenergic signals that decrease pain transmission in the dorsal spinal cord. There have been many clinical trials of perioperative gabapentin to reduce pain after surgery. Gabapentinoids reduce opioid consumption and postoperative pain scores by as much as 50%.[12–15] Long-term benefits of the perioperative gabapentinoids are less established, but there are sufficient data to warrant

their use in populations at high risk for chronic postoperative pain, including patients in whom nerves are deliberately being cut, manipulated, or repaired.

Perioperative Gabapentin: Effect on Chronic Pain

The studies assessing the effect of perioperative gabapentin on persistent postsurgical pain have been limited by small sample size, limited follow-up, and widely varying regimens. As of February 2012, the authors identified 12 distinct clinical trials examining the effect of perioperative gabapentin on pain at least 1 month after surgery (▶Table 2). Eight of these trials demonstrated at least somewhat positive results. The best results were in studies with higher doses of preoperative gabapentin (1,200 to 1,800 mg), which demonstrated a reduced incidence of persistent pain and generally lower pain scores in those with pain.[16–19] Two studies administered lower doses of gabapentin (300 to 400 mg) preoperatively and noted a reduced incidence of burning pain 3 to 6 months after surgery without reducing overall pain scores.[16,17] The four trials that failed to identify any positive benefit in long-term pain with gabapentin were all underpowered.[18–21] In sum, the existing studies suggest that higher preoperative and additional postoperative doses may be more likely to reduce the development of chronic postsurgical pain. Larger studies with improved patient retention are needed to define the optimal dosing and duration of perioperative gabapentin treatment.

Perioperative Pregabalin: Effect on Chronic Pain

Pregabalin is a newer gabapentinoid. As of February 2012, only three studies assessed long-term effects of pregabalin on postsurgical pain.[22–24] Of these, two studies identified a significant benefit to using pregabalin,[25,26] and one failed to find any effect.[27] The studies that found long-term benefit to pregabalin administered 300 mg of preoperative pregabalin and gave at least two postoperative doses. The best-powered study was conducted by Buvanendran et al, who randomized 240 people to receive either placebo or pregabalin 300 mg preoperatively and 150 mg twice a day for the first 10 days after total knee replacement, then tapering to 50 mg twice a day before stopping on postop day 14. Range of motion was improved in the pregabalin group at 30 days after surgery, and the incidence of chronic postsurgical neuropathic pain was reduced in the pregabalin group (0%) compared with the placebo group (8.7% and 5.2% at 3 months and 6 months respectively; $p = 0.001$ and $p = 0.014$).[25]

Optimal Dosing Strategies for Perioperative Gabapentinoids

Issues of Timing

It is unclear whether or not gabapentinoids are more effective when administered preoperatively versus postoperatively. Some studies[28–30] have found no or little difference between the dosing strategies in reducing postoperative pain. In one exception, it was found that individuals administered gabapentin postoperatively used significantly less patient-controlled analgesia (PCA) morphine than those given preoperative gabapentin. However, most studies using preoperative gabapentinoids administered the drugs between 1 and 2 hours prior to surgery (likely based on peak plasma level data). However, because cerebrospinal fluid (CSF) peak levels may occur much later,[31] future studies may need to employ an earlier dosing to observe the full benefits of preoperative administration.

Issues of Medication Quantity

Several studies have examined the optimal dosage of preoperative gabapentinoids for preventing early postoperative pain and reducing opioid use.[29,32,33] These studies generally indicate that higher dosages of gabapentin (900 mg or more) are more effective than lower dosages (600 mg or less). Larger dosages of pregabalin (300 mg or larger) have also been found to be more effective than lower dosages.[22,23] Based on the available literature, we recommend the following for patients at risk of severe postoperative acute pain or chronic pain: (1) giving gabapentin 1,200 mg or pregabalin 300 mg at least 2 hours prior to surgery and (2) continuing postoperatively for 14 days with pregabalin 150 mg twice a day or gabapentin 400 to 600 mg three times a day. Postoperative gabapentinoids should be decreased or stopped for postoperative sedation, dizziness, or confusion. Further definition of uncommon side effects, and the optimal preoperative dose, postoperative dose, and timing of doses is needed before perioperative gabapentinoids can be recommended as the standard of care for all patients.

Perioperative Ketamine

Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, which has been used as a general anesthetic and short-acting analgesic.[24,28,29] The NMDA receptor plays a key role in activating and sensitizing pain-carrying neurons in the dorsal horn of the spinal cord. NMDA receptor–dependent changes may participate in making pain-carrying neurons permanently hyperexcitable, contributing to chronic pain. When given at the time of injury, ketamine may decrease pain by blocking the NMDA pathway.[24,28,29]

The question of the long-term benefits of perioperative ketamine on long-term pain is unclear.[18,34–43] A study of rectal carcinoma resections found that higher-dose perioperative intravenous ketamine reduced the incidence of persistent pain at 2 weeks, 1 month, and 6 months following surgery.[30] Perioperative ketamine improved rehabilitation after total hip surgery 1 month after surgery and decreased the prevalence of postoperative chronic pain 6 months after surgery. Another study showed perioperative ketamine in chronic opioid–consuming patients reduced average pain intensity 6 weeks after surgery.[44] This study suggests that intraoperative ketamine may reduce chronic pain in chronic opioid users, who can present a challenge for postoperative pain control.

There is some evidence that dosing of ketamine is important. A large study of microdosing of ketamine in the PCA did not effect either acute or chronic pain.[32] Whereas other studies with higher doses of ketamine added to morphine PCA found improved pain control with fewer opioid-related side effects.[33,45]

In summary, low-dose perioperative ketamine results in improved immediate postoperative analgesia and opioid-sparing effects. Furthermore, this intervention is one of the few evidence-based ways for improving pain control in chronic opioid–consuming patients. The available data suggest that subanesthetic intravenous (IV) ketamine given intraoperatively may reduce the incidence of chronic post-surgical pain. A note of caution is indicated from a recent study of 100-hour ketamine infusions for pain relief in complex regional pain syndrome (CRPS), which was discontinued prematurely due to the development of possible

drug-induced liver injury in two patients and liver injury of unclear etiology in a third patient.[46]

Perioperative Antidepressants

The dorsolateral funiculus of the spinal cord carries descending noradrenergic inhibitory signals from the brain to pain synapses in the dorsal horn of the spinal cord. The brain therefore is constantly modulating the amount of pain an organism can feel. These descending signals are thought to be responsible for the reports from many trauma victims that their wounds are often not felt to be painful during the initial life-threatening phase of injury but are only felt as painful at later time points (e.g., President Reagan reported believing he had not been shot and felt no pain immediately following his attempted assassination). Tricyclic antidepressants, venlafaxine (Effexor, Wyeth Pharmaceuticals Inc.), and duloxetine (Cymbalta, Eli Lilly, Indianapolis, IN) increase synaptic availability of norepinephrine and, to varying degrees, of serotonin by inhibiting reuptake of these neurotransmitters. These drugs thereby augment descending noradrenergic inhibitory signals from the brain that reduce pain transmission in the spinal cord.

Tricyclic Antidepressants

Among antidepressants, tricyclic antidepressants have been most examined in the perioperative environment but have been examined only with regard to their effect on acute pain and opioid use—not their effect on chronic pain. This limitation is important, because animal studies suggest that perioperative amitriptyline has a long-term protective effect on pain following nerve injury.[9] Human data have been mixed. Antidepressants that more potently inhibit serotonin reuptake (amitriptyline and fluoxetine) have resulted in more pain or diminished response to opioids early after surgery.[47,48] In contrast, perioperative desipramine (a more potent reuptake inhibitor of norepinephrine) appears to significantly improve the efficacy of opioid analgesia.[34,35,49] In summary, the effect of tricyclic antidepressants on chronic postoperative pain has not been examined in humans. In the immediate postoperative time frame, perioperative desipramine seems to enhance analgesia, but perioperative fluoxetine and amitriptyline appear to augment pain on postoperative day one and two. Therefore, perioperative tricyclic antidepressants cannot be recommended at this time.

Venlafaxine and Duloxetine

In one study, 150 patients scheduled for either partial or radical mastectomy with axillary dissection were randomized to receive either venlafaxine 37.5 mg, gabapentin 300 mg, or placebo for 10 days starting the night before surgery. At 6 months, venlafaxine reduced pain scores with movement by nearly 50% compared with both placebo and gabapentin ($p < 0.0001$). Opioid analgesic use was also significantly decreased by venlafaxine compared with both placebo and gabapentin. Although the dose of gabapentin used in this study (300 mg/day) was quite low compared with other studies of perioperative gabapentin use, the dose of venlafaxine used was also quite low.[16] We were only able to identify one study of perioperative duloxetine examining whether it prevents chronic pain following surgery as of February 2012.[36] In this small, underpowered study, at 3 and 6 months following surgery there were nonsignificant trends toward diminished pain and diminished abnormal

sensations among the patients who received duloxetine. Further studies of antidepressants with significant norepinephrine reuptake inhibition should be done, including comparison of venlafaxine and duloxetine. Until then, based on the currently available evidence, venlafaxine 37.5 mg should be considered to be started the day before surgery and continued for 10 to 14 days in patients at high risk of developing chronic postsurgical pain.

Epidural and Intrathecal Local Anesthetics

Several studies have highlighted a role for epidural or spinal local anesthetics in improving acute postoperative pain control, but the long-term effect of these interventions on the development of chronic postsurgical pain remains controversial.

There have been attempts to study the role of regional anesthesia in blocking the progression of acute to chronic pain. Kairaluoma et al[37] compared preoperative placement of a paravertebral block with 0.5% bupivacaine versus a sham block in patients undergoing breast surgery and found the block group experienced improved pain acutely and on follow-up at 1, 6, and 12 months.[38]

The prevalence of postthoracotomy pain is reported to be as high as 80% at 3 months.[39] In a trial of 70 patients undergoing thoracic surgery, initiation of a continuous epidural block with mepivacaine prior to surgical incision was associated with decreased pain at 3 and 6 months when compared with epidural analgesia performed after the completion of surgery.[40] Other studies have supported the findings that preoperative block reduced chronic pain.[50,51] Taken together, these studies highlight the potential role of epidural analgesia to both reduce severe postoperative pain and perhaps more importantly prevent the subsequent development of chronic pain.

Vitamin C

Vitamin C is a free radical scavenger that has decreased tumor necrosis factor alpha (TNF α) and interleukin-6 (IL-6) in experimental models of inflammation. Zollinger et al first reported that 500 mg of vitamin C for 50 days was superior to placebo in preventing the occurrence of complex regional pain syndrome following wrist fracture.[41] They subsequently found that 500 mg per day and 1,500 mg per day dosing were superior to lower doses[42,43] Besse et al[52] reported the results of a quasi-experimental study of perioperative vitamin C in cohorts of patients undergoing foot and ankle surgery. Before the use of vitamin C, 9.6% of cases developed CRPS compared with 1.7% of patients developing CRPS following the institution of perioperative vitamin C. In summary, only three studies have examined the potential impact of vitamin C on the development of complex regional pain syndrome. However two of these were placebo-controlled, blinded, and randomized trials of high methodological quality. In all three studies vitamin C reduced the risk of developing chronic pain and CRPS. There appeared to be a dose-response relationship, with 500 mg of vitamin C per day appearing to be sufficient. Although this work clearly has to be repeated by other authors and in other settings, and particularly with controlled trials in the perioperative setting, the potential benefit when weighed against the known safety of vitamin C at this dose argues for including vitamin C in a perioperative treatment plan.

Clonidine

Clonidine is an α-2 adrenergic receptor agonist that has several pathways by which it may reduce pain.[53–60] It has both central and peripheral actions, which leads to analgesia following diverse routes of administration.[61–64] Spinal (intrathecal and epidural) clonidine appears to be more effective with fewer hypotensive side effects than intravenous clonidine. When given in combination with either local anesthetic or opioid, spinal clonidine reduces early pain and postoperative opioid requirements, and it also prolongs the time needed until first rescue analgesic.[62,63,65]

Several studies have examined the effect of perioperative clonidine on long-term pain. In a small, nonrandomized, nonblinded study of patients undergoing lower limb amputation, stump pain and phantom pain were dramatically reduced at both 6 months and 1 year in the group receiving epidural bupivacaine, clonidine, and diamorphine,[50] Lavand'-homme et al studied patients undergoing colon resection. Continuous infusion of analgesics belonging to the same class (including clonidine) was administered by either intravenous or epidural route before incision until 72 hours after surgery. They found that patients who received epidural analgesia including clonidine versus intravenous administration of clonidine at any time point (during or after surgery) demonstrated markedly less need for supplemental analgesics; reduced skin surface area that was hyperalgesic, and reduced pain at both 6 months and 1 year following surgery.[51] These results suggest that (1) multimodal epidural analgesia including epidural clonidine reduces postoperative pain, hyperalgesia, and residual pain, and (2) multimodal epidural analgesia is more effective when started intraoperatively rather than postoperatively.

Another study randomized 60 patients undergoing a right colon resection to receive 300 μg of clonidine, 10 mg of bupivacaine, or saline intrathecally prior to surgery.[66] Intrathecal clonidine significantly reduced PCA morphine use compared with both intrathecal bupivacaine and saline, and no patients in the intrathecal clonidine group experienced residual pain 6 months following surgery compared with six patients in the group that had received intrathecal saline ($p < 0.05$). It should be noted that intrathecal clonidine (300 μg) has been associated in other studies with a higher rate of postoperative sedation, and adverse hemodynamic changes. Using bispectral index monitoring to ensure the correct depth of anesthetic may help anesthesiologists prevent intraoperative and postoperative hypotension in those patients who had received clonidine.

In summary, three small prospective studies indicate that clonidine perioperatively may help prevent chronic pain following surgery. Spinal administration of clonidine appears to be more effective than systemic administration of clonidine and appears to be more effective when accomplished prior to incision rather than postoperatively.

Perioperative Interventions with Evidence for Reducing Acute Pain, but of Unknown Efficacy in Reducing the Progression from Acute to Chronic Pain

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) possess anti-inflammatory and analgesic properties that inhibit spinal and peripheral cyclooxygenase (COX-1 and COX-2) enzymes needed for the production of prostaglandins.[67] NSAIDs are useful adjuncts in multimodal analgesia and a Cochrane review demonstrates efficacy among NSAIDs when given even as a single-dose for reducing acute postsurgical pain.[68,69] Moreover, meta-analyses demonstrate that NSAIDs not only reduce postoperative pain scores but also reduce opioid consumption and show that when they are given in conjunction with opioids, they reduce postop pain, nausea, vomiting, and sedation.[70–73] COX-2 inhibitors appear to be equally effective as nonselective NSAIDs.[74] Meta-analyses of COX-2 inhibitors demonstrate more effective acute postoperative analgesia than placebo with no increase in adverse events.[75–77]

Preventative effects of NSAIDS on the progression of acute to chronic pain have not been well studied. In a randomized controlled trial of patients undergoing total knee replacement, celecoxib demonstrated 30% lower pain scores during the first 4 weeks after surgery and lower morphine consumption after surgery, but no effect was seen on pain or subjective outcome at 1-year follow-up.[78] A well done highly powered study randomized 902 patients who had undergone hip replacement to receive placebo or 400 mg of ibuprofen three times a day starting within 24 hours of completing surgery and continuing for 14 days. No significant differences in chronic pain were observed 6 and 12 months after surgery.[79] Perioperative nonsteroidal NSAID has also failed to demonstrate a reduction in the incidence of postmastectomy pain syndrome in one small trial of 30 patients at 12 months.[80]

In summary, there are good data that both nonselective NSAIDs and COX-2 inhibitors reduce pain in the immediate postoperative period. However, the available data indicate that any protective effect of postoperative ibuprofen for preventing chronic pain is clinically insignificant if it exists at all.

Acetaminophen

Acetaminophen is a commonly used nonopioid analgesic. Its mechanism of action remains unclear, though it may inhibit central cyclooxygenase transcription.[67,81] Oral acetaminophen provides effective analgesia for acute postoperative pain and reduces opioid requirements.[72,82,83] For acute pain, combining acetaminophen with NSAIDs is considered more effective than acetaminophen alone.[84] However, evidence for prevention of postsurgical chronic pain is lacking.

Glucocorticoids

Glucocorticoids are routinely administered perioperatively for their antiemetic effects,[85] but they also have important analgesic effects. They reduce proinflammatory cytokines and increase anti-inflammatory cytokines. This may reduce the development and maintenance of central sensitization and neuropathic pain associated with nerve injury.[86]

Increasing evidence suggests glucocorticoid administration may augment acute pain relief following minor and ambulatory surgical procedures.[87–89] Of particular interest is the suggestion that dexamethasone may also have an additive effect when used in combination with a gabapentinoid.[90]

Examination of the effects of perioperative single-dose dexamethasone on acute postoperative pain and opioid consumption were recently reviewed. Analgesic benefit was observed in even low-dose dexamethasone. This group concluded that dexamethasone, at doses > 0.1 mg/kg, is an effective adjunct in acute postoperative pain relief,[91] and it does not increase complications such as wound infection.

In summary, glucocorticoids appear to have a significant role in reducing acute pain and opioid use immediately following surgery. However, at this point, data are lacking to support the use of perioperative glucocorticoids to prevent the progression from acute to chronic pain.

Systemic Lidocaine

Lidocaine is a sodium channel blocker and local anesthetic.[92] Intravenous lidocaine given intraoperatively reduces immediate postoperative pain. A recent meta-analysis of 29 randomized controlled trials of IV lidocaine infusions during general anesthesia showed significantly reduced pain at rest and at 6 and 12 hours after surgery. Also, IV lidocaine reduced postoperative opioids, time to first flatus/feces, nausea/vomiting, and hospital length of stay. Although incidence of cardiac and neurologic events was comparable, 8 of 12 studies reported toxic plasma levels of lidocaine.[93]

Abdominal surgery was strongly associated with benefit from IV lidocaine.[94] A study of elective surgery for colon resection patients randomized thoracic lidocaine epidural analgesia and IV saline, or an equivalent amount of lidocaine intravenously and epidural saline, or IV and epidural saline. Thoracic epidural analgesia with lidocaine resulted in the most pain relief but the IV lidocaine was more effective than placebo.[95] thus IV lidocaine is a good alternative in patients unable or unwilling to receive an epidural catheter.

In summary, perioperative IV lidocaine appears effective in certain patient populations to reduce immediate postoperative pain and opioid requirements. Specifically, patients undergoing major abdominal procedures appear to receive the greatest benefit. Epidural lidocaine appears to be superior to intravenous lidocaine, but both are better than placebo. However, there do not appear to be any studies testing whether intravenous lidocaine reduces the likelihood of chronic postsurgical pain.

Topical Interventions

EMLA cream has shown some promise as an adjunct treatment for perioperative pain. In one trial of preoperative EMLA cream to prevent postoperative pain following breast surgery, EMLA cream did not reduce acute pain during the first 24 hours following surgery. However analgesic consumption during the second through fifth days following surgery was less in the EMLA cream group. Three months after surgery, EMLA reduced the incidence of chronic pain by 50% ($p < 0.002$).[96]

Wound infiltration with anesthetic also has also been reported to reduce chronic postsurgical pain. A trial of craniotomy patients randomized to wound infiltration with 0.75% ropivacaine or to not have wound infiltration found that the ropivacaine group had reduced pain acutely, and dramatically reduced the prevalence of persistent pain 2 months postprocedure.[97] A similar small study of the application of bupivacaine to iliac crest donor site indicated that local anesthetic infiltration in addition to morphine at the graph site reduced long-term pain 12 weeks following surgery.[98] This data suggests that wound infiltration with anesthetic may reduce chronic postoperative pain and is concordant with rat studies suggesting local anesthetic application to acute injured nerves has long term benefits.[5]

Conclusions

Many animal and human studies now suggest that preventing chronic postsurgical pain is within our grasp. A fundamental problem in the human clinical trials defining effective interventions to prevent chronic postsurgical pain is that only a minority of patients from even the most painful surgeries progress to develop chronic pain. As a result, to be adequately powered to reliably show a statistically significant difference in the rates of chronic postsurgical pain (or conversely to be convincing that a given intervention does not work) clinical trials in this area need to go from having tens of patients per trial arm to having hundreds (or thousands) of patients per trial arm. It is truly time to see the advent of multicenter clinical trials sponsored by the National Institutes of Health to address this major public health concern. These trials should aim to address proof of concept first, and then go on to define optimal doses, durations of treatment, and optimal timing of initiating individual treatments. Future work can then begin to address optimal combinations of treatments, and develop a framework for personalizing these combinations to a given patient and a given surgery.

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Table 1

Summary of recommendations for reducing the risk of chronic postsurgical pain

1) Give a gabapentinoid
Gabapentin (Pfizer, Vega Baja, PR; Neurontin) 1,200 mg 2 hours pre-incision; 400–600 mg three times a day for 14 days postoperatively. **Or** Pregabalin (Lyrica; Pfizer; capsules, Vega Baja, PR; oral solution; Kalamazoo, MI) 300 mg 2 hours pre-incision; 150 mg twice a day for 14 days following surgery. If not given before surgery, begin immediately postoperatively or after incision via a nasogastric tube intraoperatively. Lower doses appear to be helpful, but less than the doses recommended here.
2) Ketamine
Pre-incision intravenous bolus 0.5 mg/kg followed by intravenous infusion 0.25 mg/kg /hour. This intervention should not be done for patients with known liver disease or with significant risk factors for liver disease (e.g., alcoholism).
3) Make it numb
Initiate regional anesthesia with a regional block or an epidural before incision. **Or** Infiltrate ropivacaine 0.75% 20 mL in the wound (n.b., if given in conjunction with a regional block using conventional dosages or accidentally injected intravenously, this ropivacaine dose is sufficient to induce severe local anesthetic toxicity). **Or** Apply 20 g of EMLA (eutectic mixture of local anesthetics) cream around the site of the wound preoperatively 5 minutes before surgery and daily for the first 4 days following surgery.
4) Give venlafaxine (Effexor XR, Wyeth Pharmaceuticals Inc., Philadelphia, PA)
37.5 mg of extended-release venlafaxine starting the day before surgery and continuing for 10 to 14 days following surgery (n.b., this may not be appropriate in patients already taking other antidepressants).
5) Vitamin C
500 to 1,000 mg for 50 days following surgery, based on known safety and efficacy in preventing complex regional pain syndrome following wrist fracture and foot and ankle surgery.

Table 2

The effectiveness of perioperative gabapentin for chronic pain

Positive Studies				
Surgery type	**Patients**	**Most remote follow-up**	**Positive findings**	**Negative findings**
Abdominal hysterectomy[99]	25	1 month	Gabapentin reduced incidence of pain 1 month after surgery.	Did not identify a statistically significant decrease in immediate postoperative pain
Inguinal herniorrhaphy[100]	30	6 months	Gabapentin reduced pain scores at 1, 3, and 6 months after surgery. The number of patients with daily activity adversely affected by pain was lower in the gabapentin group at 1 month.	The number of patients whose daily activities were adversely affected by pain was similar between groups at 3 months and 6 months
Abdominal hysterectomy[101]	20	6 months	Gabapentin reduced pain scores, pain impact, and incidence of pain at 1, 3, and 6 months.	Pain impact on activities of daily living was not significantly different at 6 months
Thyroidectomy[102]	23	6 months	Gabapentin reduced total pain score and the incidence of more intense pain at 6 months.	Nonsignificant trend toward decreased burning sensation and numbness in the gabapentin group.
Mastectomy[16]	50	6 months	At 6 months gabapentin reduced the incidence of burning pain.	Gabapentin did not reduce global pain severity and opioid use at 6 months.
Breast cancer surgery[17] **	22	3 months	Gabapentin and mexiletine each reduced the incidence of burning pain at 3 months.	Gabapentin did not reduce the incidence of chronic pain, or patients requiring analgesics at 3 months.
Breast cancer surgery[103] **	20	6 months	Gabapentin reduced the incidence of chronic pain and analgesic use at 3 months.	Gabapentin did not reduce the incidence of chronic pain, and analgesic use at 6 months.
Abdominal hysterectomy[104]	27	1 month	Gabapentin reduced the incidence of pain at 1 month.	Gabapentin did not reduce the incidence of analgesic use at 1 month.
Negative Studies				
Surgery type	**Patients** *	**Most remote follow-up**	**Positive findings**	**Negative findings**
Coronary artery bypass graft surgery[18]	20	3 months	Gabapentin reduced pain intensity immediately after surgery	Gabapentin did not reduce pain intensity at 1 month and 3 months.
Total hip arthroplasty[19]	28	6 months	None	Gabapentin did not reduce pain at any time point (one third of patients lost to remote follow-up).
Cesarean delivery[20]	16	3 months	Gabapentin improved acute but not chronic pain.	Gabapentin failed to reduce persistent pain, or median pain scores at 3 months.
Lower limb amputation[21]	15	6 months	None	Gabapentin failed to reduce the incidence and intensity of pain at 6 months.

* Indicates the number of gabapentin patients per group available for most remote follow-up.

** Modified radical mastectomy or lumpectomy with axillary lymph node dissection.