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Chronic postsurgical pain after nonarthroplasty orthopedic surgery

Sugantha Ganapathy, FRCA, FRCPC, Jonathan Brookes, FRCA

From the Department of Anesthesiology and Perioperative Medicine, London Health Sciences Centre, University Hospital, University of Western Ontario, London, Ontario, Canada.

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Chronic postsurgical pain (CPSP) following nonarthroplasty orthopedic surgery has a variable incidence and results in significant morbidity in patients. The etiology of this persisting pain could be because of a variety of insults during surgery including injuries to nerves and release of inflammatory mediators. Trauma is well known to result in complex regional pain syndrome (CRPS). Phantom limb pain frequently follows both traumatic and ischemic amputations. Both these conditions are well known to result in debilitating pain. Management of CPSP is not only dependent on careful planning of acute pain management but also the treatment of established pain. Preventive strategies include use of multimodal analgesia, preventing opioid-induced hyperalgesia, and use of regional blocks. Treatment of established CPSP will depend on its etiology. Phantom pain and CRPS can be difficult to treat once established. Many therapeutic interventions have been tried with variable success.

Chronic postsurgical pain (CPSP) is a well-known clinical entity following many common operations, including breast surgery, spinal surgery, thoracotomy, cholecystectomy, inguinal hernia repair, post trauma surgery, and joint arthroplasty.

This article focuses on CPSP following orthopedic surgery not involving arthroplasty procedures. This subset of CPSP can result from a wide range of common procedures such as surgery on spine, tendon repair/reconstruction, amputations, arthroscopies, open reduction and internal fixation of bones following trauma, and fusion of joints. This article covers the incidence of CPSP following these procedures, its etiopathogenesis, therapeutic interventions for its prevention, and therapeutic interventions once the pain is established. The common causes for CPSP following such procedures include nerve injuries, complex regional pain syndrome types 1 and 2, phantom pain, and poorly controlled acute pain.

Address reprint requests and correspondence: Sugantha Ganapathy, FRCA, FRCPC, Professor, Director Regional and Pain Research, Department of Anesthesiology and Perioperative Medicine, University of Western Ontario, Room B3213 London Health Sciences Centre, University Hospital, London, Ontario N6A 5A5, Canada.
E-mail address: Sugantha.Ganapathy@lhsc.on.ca.

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Incidence

Chronic postsurgical pain has received increasing attention in the literature in recent years. The substantial morbidity borne by patients and the burden placed on chronic pain services have been demonstrated by publications that show a surprisingly high incidence of CPSP following relatively minor and common surgical procedures.

Before the incidence of CPSP can be discussed, the condition must be defined. Mccrae[1] was the first to suggest working diagnostic criteria for CPSP. It is accepted by the International Association for the Study of Pain that to qualify as CPSP the following criteria must be fulfilled:

i. The pain should have developed after a surgical procedure;

ii. The pain should be of at least 2 months' duration;
iii. Other causes for the pain should have been excluded;
iv. The possibility that the pain is continuing from preexisting problems must be explored and exclusion attempted.

The last criterion can make estimations of the incidence of CPSP difficult. Many operations are performed to relieving pain, and it can therefore be difficult to distinguish, even with prospective studies, ongoing pain secondary to the original pathology from CPSP. On the contrary, CPSP following surgeries such as iliac crest bone graft is clearly because of the procedure itself, as no preexisting pathology at the donor surgical site existed. For all other operations, it is impossible to be absolutely sure that a preexisting problem has not made a contribution to CPSP, and many studies do not even attempt to make this distinction.

Gehling et al[2] in a prospective cohort study interviewed 201 patients 7 months after elective trauma surgery. The sample covered a wide mix of procedures (Table 1), and it is not possible from the published results to establish the incidence of CPSP following individual procedures, but the results clearly show a significant level of chronic pain following a variety of relatively minor operations. The authors graded the pain on a scale of 0 to IV as follows: grade 0 = pain free; grade I = low pain intensity and low pain-related disability; grade II = high pain intensity and low pain-related disability; grade III = high pain-related disability and moderately limiting; and grade IV = high pain-related disability and severely limiting. In their group, 38.4% fell into the grade I category, 7.5% into grade II, and 20.2% into grades III and IV. Thus, obviously CPSP following nonarthroplasty orthopedic surgery is not a trivial problem.

Stiglitz et al[3] performed a prospective case series of 231 patients to assess pain after shoulder arthroscopy. Post discharge pain was evaluated using a questionnaire after 1 week, 1 month, and 1 year. The anesthetic and analgesic techniques varied widely from performed either under general anesthesia or under interscalene block. Analgesic interventions included a single subacromial injection, a subacromial catheter, an intra-articular catheter, or no interventional supplementation. Operative procedures performed were also widely varied (Tables 2 and 3). The study showed that pain values remained relatively low (<4/10) at all time points following most shoulder arthroscopic surgeries and the immediate postoperative pain scores had no correlation to pain at 1 year.

In terms of pain levels and analgesic technique, the authors found lower levels of postoperative pain on the day of operation and first postoperative day with the interscalene catheters compared to the other local anesthetic techniques, but no difference was found between groups from day 2 onward. This is in significant contradiction to other publications. Unfortunately no firm conclusions can be drawn from this case cohort in view of multiple uncontrolled variables in pain management. One obvious factor is that arthroscopic surgery results in lower degrees of pain. In a large patient survey of 5130 patients attending pain clinics in Scotland and northern England, Crombie et al in 1998[4] documented that surgery was the main contributing factor to pain in 22.5% of patients. It was not possible to identify individual surgical categories from this series.

Andersen et al[5] followed up 109 patients after low back surgery who had been previously randomized to surgery with or without instrumentation using a questionnaire 5 years after surgery. All patients had iliac crest bone grafting done. In this study, 10% of patients still experienced pain at the bone graft donor site (a site one could reasonably as-

Table 1 Making the diagnosis

Talofibular ligament suture	12 (6%)
Arthroscopy	36 (17.9%)
Muscle or tendon suture	10 (4.5%)
Tibia osteosynthesis	25 (12.4%)
Ankle osteosynthesis	37 (18.9%)
Femoral osteosynthesis	11 (5.5%)
Foot joint reconstruction	11 (5.5%)
Open knee surgery	13 (6.5%)
Hip TEP/osteosynthesis	12 (6%)
Radius osteosynthesis	11 (5.5%)
Humerus osteosynthesis	8 (4.5%)
Shoulder reconstruction	6 (3%)
Olecranon reconstruction	2 (1%)
Other operations	7 (3.5%)

Reproduced from Gehling et al.[2]

Table 2 Types of surgery performed

Type of arthroscopy	Number of cases
Decompressive	122
Repair	78
Instability	20
Other	11

Adapted from Stiglitz et al.[3]

Table 3 Type of intervention

	Number of cases
Rotator cuff repair	78
Calcifying tendinopathy	31
Acromioplasty	164
Acromioclavicular resection	27
Bicipital intervention	91
Tenotomy	53
Tenodesis	38
Anterior stabilization	20
Other procedure	11
Exploration (including 1 with total prosthesis)	4
Glenohumeral arthrolysis	3
Ablation of osteosynthesis material	1

Adapted from Stiglitz et al.[3]

sume to be previously pain free). Although 75% of patients still suffered back pain, one cannot assume that all the pain is CPSP because a significant proportion of patients would have had preoperative back pain. Similarly, Robertson and Wray[6] in a prospective study that looked at the natural history of iliac crest bone grafting for spinal surgery found 12% of patients at 12 months had a pain score of over 3/10 on a visual analog scale.

Schwartz et al[7] in a prospective study of 170 patients undergoing spinal fusion surgery with autologous iliac crest bone grafting found 19% of patients experienced donor site pain after a mean follow-up period of 3.5 years. Singh et al,[8] in one of the relevant albeit small randomized controlled trial in this field, compared acute pain scores between two groups of patients undergoing iliac crest bone grafting after posterior spinal arthrodesis. They randomized 26 patients to receive 48-hour wound infusion of bupivacaine or placebo at the graft donor site and followed them for 4 years. At 4 years, 82% of the experimental group and 72% of the control group could be contacted. The pain scores at 4 years at the donor site were significantly lower in the treatment group (1.4 vs 4.8/10) and no patient in the treatment group developed dysesthesia at the donor site, whereas 70% of patients in the control group had dysesthesia at the donor site at this time point. In a study of 208 patients comparing bone morphogenic protein to Iliac Crest Bone Graft (ICBG), Sasso et al[9] noted that 31% of patients undergoing ICBG experienced ongoing pain at the graft donor site at 24 months.

Wong et al[10] used a questionnaire to survey 105 patients following scoliosis surgery involving ICBG. Scoliosis surgery is often not done for preexisting pain but to halt progression and prevent complications of scoliosis. As a result, this is one of the few articles that give us an insight into CPSP following back surgery. They note that 6.7% of patients suffered pelvic pain beyond 12 months, presumably from the donor site, and that 10% of patients suffered back pain persisting beyond 12 months.

Phantom limb pain (PLP) is that which occurs in a body part that is no longer present[11] and is a major cause of morbidity in amputees. It is important to distinguish PLP from pain in the stump and phantom sensation. Estimates of incidence of PLP vary widely but more recent studies give figures from 72% (81% for lower limb amputations)[12] to as high as 92%.[13] This pain may start as late as a year after the amputation.

Etiopathogenesis

Contributing factors for developing CPSP include injury to nerves at the time of surgery from incision or tourniquet, inflammatory response because of surgery both locally and neuraxially, as well as development of complex regional pain syndromes, the etiology of which can be variable.

In order for CPSP to develop, changes must occur in the sensory nervous system. The ability of the nervous system to change in this manner is termed neuroplasticity,[14] and there are three major mechanisms. According to Woolf, the pioneer in basic science of pain, the first of these, "activation-dependent plasticity," occurs in nociceptive pathways. This may occur because of changes in the nociceptors themselves or in the dorsal horn. When the change occurs in the nociceptors, there may be reduction of threshold for activation either because of the repeated activation by the relevant stimulus (heat, pressure, and chemicals) or by stimuli that do not actually activate the nociceptor. When the change occurs in the dorsal horn, strong stimuli such as severe pain act to cause fast excitatory postsynaptic potentials, which lead to temporal summation and a decrease in threshold potential. This decrease in threshold may be made more profound by *N*-methyl-D-aspartate (NMDA) receptor activation. Normally, the activation-dependent neuroplasticity does not persist once the initial stimulus is removed.

The second type of neuroplasticity is called "modulation." This occurs secondary to inflammation and release of inflammatory cytokines and chemicals and leads to phosphorylation of receptor, ion channel, or regulatory proteins. This phosphorylation alters the functional properties or expression of cell surface channels. It is therefore described as "posttranslational" as it affects existing proteins. It can occur at the peripheral terminals of nociceptors, where it causes primary hyperalgesia, or in the dorsal horn of the spinal cord, where it can cause secondary hyperalgesia,[15] ie, hyperalgesia outside the area of the initial stimulus. These changes last for a longer period than activation-dependent neuroplasticity but are still reversible.

"Modification" (Woolf) is the final category of neuroplasticity and is due to the altered expression of proteins such as ion-channels, G-protein-coupled receptors, structural proteins, and neurotransmitters. The changes occur in the level of target-derived growth factors reaching the neuron. These factors increase in inflammation and decrease with axonotmesis as the neuron is functionally separated from its target, such as following nerve injury. These changes can again occur in primary sensory neurons and, via microglia-mediated signaling mechanisms, dorsal horn neurons, leading to primary and secondary hyperalgesia, respectively. This type of neuroplasticity may cause very long-lasting effects.

Glial cells found in the spinal cord have been strongly implicated in the development of chronic pain. Proliferation of glial cells and increased phosphorylation of glial p38 mitogen-activated kinase occurs after nerve injury, chronic exposure to opioids, and surgical incision.[16] This activation of p38 can persist as late as 3 weeks. Signals traveling via large myelinated Aβ fibers have been also implicated in the activation of p38 as blockade of the sciatic nerve in rats has been shown to prevent such activation.[16,17] Proinflammatory cytokines, interleukin-1β, interleukin-6, and tumor necrosis factor-α, are all released following activation of p38 kinase. All these cytokines have been shown to produce hyperalgesia and allodynia.[18]

Phantom pain is thought to receive contributions from peripheral and central changes. Severing nerves during amputation, particularly if associated with ligation of the nerves, has been documented to result in neuroma formation at the severed ends. These neuromas can spontaneously discharge and have low spontaneous firing thresholds. Disrupted A and C fibers result in changes at the spinal level with Aβ mechano-sensitive fibers, making contact with the exposed nociceptive layers. This Aβ fiber input may be interpreted as painful stimuli and can be worsened by other mediators such as substance P. Changes in the spinal dorsal horn lead to changes at the level of the brainstem, cortex, and thalamus. Anxiety and catecholamines may exacerbate the firing from the neuromas. In this scenario of PLP, one needs to distinguish PLP from stump pain, which could be organic, and phantom sensation. This topic has been reviewed recently by Wolff et al[11] and Flor.[19]

Complex regional pain syndrome has been categorized into two distinct entities. Type 1 follows many surgical procedures and trauma and type 2 follows specifically after nerve injury (causalgic). The diagnosis is made on predetermined criteria. The signs and symptoms include persisting pain following surgery in the affected area associated with color, trophic, and nail changes as the process continues. Often there is significant restriction of movement in the affected area. There is allodynia and hyperalgesia. Eventually these symptoms become diffuse, affecting other limbs as well. Contractures and bone demineralization often ensue because of disuse secondary to pain and rigidity. These symptoms can recur with each exposure to surgery and thus warrant active prophylactic measures. The precise etiology of this painful condition still eludes us.

Risk factors for CPSP

Determining which patients are at a high risk for developing CPSP is important to allow targeting of interventions at this group. Because only a small proportion of patients will go on to develop CPSP, if some targeting is not done prior to surgery, economic resources will be wasted and unnecessary interventions carried out.

Of all risk factors, severity of acute postoperative pain is most strongly linked to CPSP. There is not enough evidence to state with certainty that this is a causative relationship, but there is certainly a strong correlation.[2,20,21]

Preoperative pain has also been shown to be correlated with a risk of developing CPSP, as shown by Gerbershagen et al.[22] Patients with higher preoperative pain scores had higher levels of postoperative pain at the surgical site as well as pain at remote nonsurgical areas at 6 months after radical prostatectomy. These authors also note that patients with CPSP have documented poorer mental health quality of life as well as severe psychosomatic dysfunction preoperatively as well as at 3 months postoperatively. Thus, psychosocial factors can be important contributing factors to CPSP. Bachiocco et al[23] studied the role of individual pain history and family history of pain tolerance using the Minnesota Multiphasic Personality Inventory, Eysenck Personality Inventory, State Trait Anxiety Inventory, and personal interviews on postthoracotomy CPSP. They showed that those who had suffered severe medical pain previously, and had been documented to have poor familial pain models, suffered more severe postoperative pain in the early postoperative period. Considering that poorly controlled acute pain can be a predictor of CPSP, this subset of patients could be prone for CPSP. Hinrichs-Rocker et al[24] in a systematic review concluded that depression, psychological vulnerability, stress, and late return to work were all positively correlated to CPSP. Other factors, including neuroticism, low educational status, race, and gender, were not predisposing factors for CPSP. Other authors have found younger age to have a correlation with both CPSP[21,25] and prolonged acute postsurgical pain.[26] A correlation of CPSP with preoperative anxiety is common.[22,25-27]

Genetic factors also play a role in the risk of developing CPSP. A haplotype of the GCH-1 gene has been described by Tegeder et al,[28] which is associated with a significant decrease in pain following lumbar discectomy; this gene was found to be upregulated less in patients homozygous for the haplotype. This gene codes for the enzyme GTP cyclohydrolase, which is the rate-limiting enzyme for the synthesis of a key modulator of peripheral neuropathic and inflammatory pain, BH4.

Obesity has been shown to have a strong association with chronic pain in patients in the community,[29] with possible mechanisms being increased mechanical stresses on lower body structures, neuromodulation secondary to a proinflammatory state, and psychological factors associated with obesity. Ray et al looked for an association with aspects of the central obesity syndrome and found central obesity to be the strongest predictor of chronic pain, with an odds ratio of 1.7.[30]

Krane and Heller[13] found high levels of phantom limb pain regardless of the cause of amputation; trauma/infection, 92%, cancer, 90%, but lower for congenital deformity, 50%. However, there were only two cases in the latter category. There was a trend toward patients with a shorter duration of preoperative pain being more likely to have their postoperative pain resolved in a shorter time.

Therapeutic interventions for prevention

One of the most obvious methods of reducing the incidence of CPSP is choice of operation (Table 4). As 1 cause of CPSP is nerve damage, a surgical approach that reduces this risk should lead to a lower risk of CPSP. Aasvang and Kehlet[31] found a lower incidence of chronic groin pain after laparoscopic inguinal herniorrhaphy compared to an open technique. Swanson in 1983[32] found a high rate of chronic dysesthesia after medial meniscectomy and attributes this to

Table 4 Preventive strategies for CPSP

1. Surgical technique
2. Pre-emptive and preventive analgesia
3. NMDA antagonists (ketamine, memantine)
4. Local anesthetic infiltration and infusion
5. Regional blocks
6. Clonidine
7. Wound and perineural infusions of local anesthetic

damage to the prepatellar branches of the saphenous nerve. Tennent et al[33] in 1998 describes similar cases of pain following knee arthroplasties, anterior cruciate ligament repair, and arthroscopy and also attributes this to damage to branches of the saphenous nerve. These authors have made suggestions regarding the surgical approach to minimize this risk. Occasionally, nerve injuries during surgeries on the elbow/shoulder and following trauma are unavoidable because of the close proximity of the nerves to the surgical site. Meticulous attention to detail to protect them is an important strategy to prevent CPSP. Some surgeries such as limb amputations inevitably result in nerves being cut, resulting in neuromas, phantom pain, and type 2 complex regional pain syndrome (CRPS).

Preemptive analgesia and its efficacy have been much debated in the literature. The meta-analysis by Cliff et al[34] that looked at acute postoperative pain showed epidural anesthesia reduced acute pain intensity scores and time to first analgesic consumption. Local infiltration analgesia and nonsteroidal anti-inflammatory drug (NSAID) administration improved only analgesic consumption and time to first analgesic. NMDA antagonists appeared to have no effect, and opioids trended toward a negative effect, not surprising in view of the acute tolerance (consistent with the phenomenon of opioid-induced hyperalgesia) described by Chia et al.[35]

Singh et al[8] have shown a clear benefit of local anesthetic infusion on CPSP rates following iliac crest bone grafting, after placing an infusion catheter at the operative site and delivering 0.5% bupivacaine for 48 hours in the experimental group and infusing saline in the control group. After a minimum 4-year follow-up period, pain scores were significantly lower and satisfaction higher in the group that received local anesthetic wound infusion.

Preventing opioid-induced hyperalgesia is another obvious goal. Large intraoperative doses of opioid have been documented to increase postoperative pain.[35] Animal data show clearly that this effect of opioids on causing Opioid Induced Hyperalgesia (OIH) can be eliminated with ketamine in rats.[36]

Ketamine is a nonspecific NDMA receptor antagonist that has been shown to have a small benefit in terms of postoperative analgesia but a much larger effect on opioid sparing.[37] This effect may occur through either pre- or postsynaptic glutamate-mediated mechanisms.[36] Laskowski et al[38] recently published a systematic review of intravenous ketamine for postoperative analgesia and found evidence of decreased opioid consumption and time to first analgesia in all 70 randomized controlled trials (RCTs) they reviewed between 1966 and 2010. In 78% of studies that these authors reviewed, patients experienced less acute pain despite this decreased opioid use. Cartensen and Moller[39] performed a qualitative review of 887 patients receiving a mixture of ketamine and morphine via patient controlled analgesia in 11 RCTs and found improved analgesia in 6 of the 11 studies. Thus, ketamine might have a role in preventing CPSP via reduction in opioid requirements as well as improved acute pain management.

Clonidine is an α-2 agonist. Cao et al[40] found a significant decrease in the proportion of children requiring rescue analgesic when 4 μg/kg was given orally as a premedicant. Michawa et al[41] found a reduction in pain scores and the need for supplementary analgesia in the immediate (2-hour) postoperative period after an oral premedication dose of 4 μg/kg for children undergoing minor surgery. De Kock et al in 2005[42] found that 300 μg of intrathecal clonidine significantly reduced morphine requirements in the first 72 hours following laparotomy compared to a saline placebo. Clonidine also reduced the area of hyperalgesia at 72 hours compared to saline placebo and intrathecal bupivacaine. They also noted less residual pain at 2 weeks, 1 month, and 6 months in the clonidine group. On the contrary, Lavand'homme et al[43] found the addition of intrathecal clonidine to patients receiving spinal anesthesia for elective Cesarean section reduced overall area and incidence of hyperalgesia at 48 hours postoperatively, but did not detect a difference in opioid requirements, acute pain scores, or residual pain at 1, 3, and 6 months. Unfortunately, there are no data on the use of these drugs in orthopedic surgery.

Prevention of phantom limb pain involves a multipronged staged approach as suggested by Wolff et al. Psychological preparation of the patient preoperatively is important. The surgical technique should incorporate not ligating the nerve but making a clean cut to prevent neuroma formation. Aggressive early treatment of pain with opioids, perineural local anesthetic infusion, and multimodal analgesia incorporating drugs such as gabapentin seems to have a positive effect in the immediate postoperative period. Unfortunately, there is a paucity of randomized prospective clinical trials of any intervention with adequate sample size.

With regards to complex regional pain syndrome, continuous peripheral nerve blocks using indwelling catheters have helped with both acute pain and symptom relief as well as managing established pain.[44] In our institution, we often initiate continuous brachial plexus blocks in anyone coming for surgery with the previous history of CRPS type 1 (Ganapathy S.).

Therapy for established pain

Management of established pain with regards to CPSP can be thought of in two phases—managing acute postsurgical

pain with the hope of reducing subsequent CPSP and managing CPSP itself.

Acute postsurgical pain is commonly targeted with opioids, but as already mentioned, this can lead to opioid-inducing hyperalgesia. A multimodal approach with the aim of reducing opioid usage would therefore seem sensible. Acetaminophen and NSAIDs have both been shown to reduce the opioid dose required in the postoperative setting. NSAIDs and COX-2 inhibitors also have the potential benefit of reducing the proinflammatory effect of the surgical stimulus both locally and on the neuraxis via the receptor expression.

Gabapentin has been the subject of a surge in interest in perioperative field in the last decade and has been the subject of many RCTs and several meta-analyses. A systematic review of gabapentin[45] demonstrated the drug's role as a treatment for acute pain. Three meta-analyses[46-48] reported decreased opioid consumption and pain scores in the early postoperative period, and the largest reported decreased nausea and vomiting rates. Two of the three meta-analyses reported increased sedation because of gabapentin used; the third showed no increase. The largest meta-analysis divided and analyzed patients into three subgroups—those receiving a single dose of gabapentin of 1200 mg preoperatively, those receiving a single dose of less than 1200 mg, and those receiving multiple perioperative doses. All three groups showed decreased cumulative doses of morphine in the first 24-hour period, and a single dose of gabapentin of 1200 mg or less significantly reduced pain scores at 6 and 24 hours.

With regards to CPSP, gabapentin has been somewhat less successful.[45] One RCT showed no effect on the overall level of pain after mastectomy. Another showed a slight increase in pain 3 months after a mastectomy or axillary clearance but no difference at 6 months, and a third RCT showed no change in incisional pain after 3 months.

Pregabalin has also been the subject of a recent meta-analysis.[49] The authors looked at levels of acute pain in the first 24 hours, time to request for first analgesia, and incidence of side effects. Doses of pregabalin below 300 mg/d resulted in decreased opioid consumption of 8.8 mg during the first 24 hours in the three studies in which these data could be analyzed, and doses above or equal to 300 mg/d showed a significant decrease in opioid use in the first 24 hours of 13.4 mg. None of the studies resulted in a significant difference in pain intensity during the first 24 hours. No difference in time to first rescue analgesia was found with any dosage regimen. Pregabalin was associated with a lower risk of vomiting (risk ratio 0.73) but a higher risk of visual disturbance (risk ratio 3.29). To date, there are no large-scale studies documenting its role or benefits with nonarthroplasty orthopedic CPSP.

Therapeutic interventions described for established phantom limb pain are numerous. These therapies could be classified into medical management and interventional therapies. Pharmacologic therapies reported so far have included the use of opioids such as tramadol or morphine,[50] amitriptyline, carbamazepine, gabapentin, intravenous lidocaine, ketamine, calcitonin, benzodiazepines, and etanercept.[51] Most of the studies reporting benefits from these drugs are anecdotal and thus need to be evaluated further in a prospective randomized fashion with adequate sample size. The interventional modalities of therapy include spinal cord stimulators,[52] deep brain stimulation, phenol injection or radiofrequency ablation of stump neuromas and dorsal root ganglia, and mirror therapy.[53]

Therapeutic interventions for established CRPS include medical management with antidepressants, corticosteroids, narcotic analgesics, calcitonin, bisphosphonates, *N*-acetyl cysteine, dimethyl sulfoxide cream, gabapentin, and tadalafil. Most of these drugs have been reported to be useful in symptom management. Interventional therapies include continuous peripheral nerve blocks, spinal cord stimulators, intravenous regional analgesia with guanethidine, sympathetic blocks such as stellate blocks, epidural clonidine, and intrathecal baclofen. This topic has been recently reviewed by De Tran et al.[54] Dadure[44] et al have reported on the successful use of continuous peripheral nerve blocks in children combined with IV regional analgesia to treat established CRPS.

Conclusions

CPSP, even after relatively minor surgical procedures, is common, with reported incidences of between 10% and 36%. Its etiology is complex, with neuroplasticity changes occurring at the level of nociceptors and presynaptic neurons and in the dorsal horn of the spinal cord. These changes include short-lived changes in existing cell protein phosphorylation, and long-lived changes in protein expression and cell structure. In animal studies, increases in microglial cyclooxygenase have been documented after surgical incision,[55] possibly causing prolonged pain.

Risk factors are numerous and should allow targeting of therapy toward those at greater likelihood of developing CPSP during preoperative interviews, leading to a potential decrease in unnecessary interventions, and a decrease in patient exposure to risk. Prominent risk factors include preoperative and acute postoperative pain, depressive disorders, prior medical pain, and history of family members coping poorly with pain, anxiety, and stress. Specific genotypes are also associated with higher risk. Preoperative analgesia is likely to play a limited but important role in prevention, as is surgical technique. Pharmacotherapeutic options that demonstrated to have been of value include prevention of opioid-induced hyperalgesia by reducing opioid requirement through use of opioid-sparing multimodal analgesia techniques and use of ketamine. Doses of ketamine required to have a significant effect on OIH have been shown to be small. Management of established CPSP should also include management of CRPS, which includes antidepressants, continuous regional analgesia, intravenous

lidocaine, and spinal cord stimulators, to mention a few. With the introduction of minimally invasive surgery, we may have to revisit management of CPSP.

References

1. Macrae WA: Chronic pain after surgery. Br J Anaesth 87:88-98, 2001
2. Gehling M, Scheidt C, Niebergall H, et al: Persistent pain after elective trauma surgery. Acute Pain 2:110-114, 1999
3. Stiglitz Y, Gosselinb O, Sedaghatiana J, et al: Pain after shoulder arthroscopy: A prospective study on 231 cases. Orthop Traumatol Surg Res 97:260-266, 2010
4. Crombie IK, Davies HT, Macrae WA: Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain 76:167-171, 1998
5. Andersen T, Christensen FB, Hansen ES, et al: Pain 5 years after instrumented and non-instrumented posterolateral lumbar spinal fusion. Eur Spine J 12:393-399, 2003
6. Robertson PA, Wray AC: Natural history of posterior iliac crest bone graft donation for spinal surgery. Spine 26:1473-1476, 2001
7. Schwartz CE, Martha JF, Kowalski P, et al: Prospective evaluation of chronic pain associated with posterior autologous iliac crest bone graft harvest and its effect on postoperative outcome. Health Qual Life Outcomes 7:1-8, 2009
8. Singh K, Phillips FM, Kuo E, et al: 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 32:2790-2796, 2007
9. Sasso RC, LeHuec JC, Shaffrey C, et al: Iliac crest bone graft donor site pain after anterior lumbar interbody fusion: a prospective patient satisfaction outcome assessment. J Spinal Disord Tech 18:S77-S81, 2005 (suppl 1)
10. Wong GT, Yuen VM, Chow BF, et al: Persistent pain in patients following scoliosis surgery. Eur Spine J 16:1551-1556, 2007
11. Wolff A, Vanduynhoven E, van Kleef M, et al: 21. Phantom pain. Pain Pract 11:403-413, 2011
12. Dijkstra PU, Geertzen JH, Stewart R, et al: Phantom pain and risk factors: a multivariate analysis. J Pain Symptom Manag 24:578-585, 2002
13. Krane EJ, Heller LB: The prevalence of phantom sensation and pain in pediatric amputees. J Pain Symptom Manag 10:21-29, 1995
14. Woolf CJ, Salter MW: Neuronal plasticity: increasing the gain in pain. Science 288:1765-1769, 2000
15. Burke S, Shorten G: When pain after surgery doesn't go away. Biochem Soc Transact 37:318-322, 2009
16. Wen Y-R, Tan P-H, Cheng J-K, et al: Microglia: a promising target for treating neuropathic and postoperative pain, and morphine tolerance. J Formos Med Assoc 110:487-494, 2011
17. Wen YR, Suter MR, Kawasaki Y, et al: Nerve conduction blockade in the sciatic nerve prevents but does not reverse the activation of p38 mitogen-activated protein kinase in spinal microglia in the rat spared nerve injury model. Anesthesiology 107:312-321, 2007
18. Kawasaki Y, Zhang L, Cheng JK, et al: Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. J Neurosci 28: 5189-5194, 2008
19. Flor H: Phantom-limb pain: characteristics, causes, and treatment. Lancet Neurol 1:182-189, 2002
20. Perkins MF, Kehlet H: Chronic pain as an outcome of surgery. Anesthesiology 93:1123-1133, 2009
21. Aasvang E, Kehlet H: Chronic postoperative pain: the case of inguinal herniorrhaphy. Br J Anaesth 95:69-76, 2005
22. Gerbershagen HJ, Ozgür E, Dagtekin O, et al: Preoperative pain as a risk factor for chronic post-surgical pain - six month follow-up after radical prostatectomy. Eur J Pain 13:1054-1061, 2009
23. Bachiocco V, Scesi M, Morselli AM, et al: Individual pain history and familial pain tolerance models: relationships to post-surgical pain. Clin J Pain 9:266-271, 1993
24. Hinrichs-Rocker A, Schulz K, Järvinen I, et al: Psychosocial predictors and correlates for chronic post-surgical pain (CPSP)—a systematic review. Eur J Pain 13:719-730, 2009
25. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: risk factors and prevention. Lancet 367:1618-1625, 2006
26. Katz J, Poleshuck EL, Andrus CH, et al: Risk factors for acute pain and its persistence following breast cancer surgery. Pain 119:16-25, 2005
27. Gerbershagen HJ, Dagtekin O, Rothe T, et al: Risk factors for acute and chronic postoperative pain in patients with benign and malignant renal disease after nephrectomy. Eur J Pain 13:853-860, 2009
28. Tegeder I, Costigan M, Griffin RS, et al: GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 12:1269-1276, 2006
29. McCarthy LH, Bigal ME, Mindy Katz MPH, et al: Chronic pain and obesity in elderly people: results from the Einstein Aging Study. J Am Geriatr Soc 57:115-119, 2009
30. Ray L, Lipton RB, Zimmerman ME, et al: Mechanisms of association between obesity and chronic pain in the elderly. Pain 152:53-59, 2011
31. Aasvang E, Kehlet H: Chronic postoperative pain: the case of inguinal herniorrhaphy. Br J Anaesth 95:69-76, 2005
32. Swanson AJ: The incidence of prepatellar neuropathy following medial meniscectomy. Clin Orthop Relat Res 181:151-153, 1983
33. Tennent TD, Birch NC, Holmes MJ, et al: Knee pain and the infrapatellar branch of the saphenous nerve. J R Soc Med 91:573-575, 1998
34. Ong CK, Lirk P, Seymour RA, et al: The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg 100:757-773, 2005
35. Chia YY, Kang L, Wang JJ, et al: Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anaesth 46:872-877, 1999
36. Celerier E, Cyril Rivat BS, Yan Jun, et al: Long-lasting hyperalgesia induced by fentanyl in rats. Anesthesiology 96:465-472, 2000
37. Elia N, Tramèr MR: Ketamine and postoperative pain—a quantitative systematic review of randomised trials. Pain 113:61-70, 2005
38. Laskowski K, Stirliing A, McKay WP, et al: A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth 2011 [Epub ahead of print]
39. Carstensen M, Møller AM: Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. Br J Anaesth 104:401-406, 2010
40. Jianping C, Shi X, Miao X, et al: Effects of premedication of midazolam or clonidine on perioperative anxiety and pain in children. BioSci Trends 3:115-118, 2009
41. Mikawa K, Nishina K, Maekawa N, et al: Oral clonidine premedication reduces postoperative pain in children. Anesth Analg 82:225-230, 1996
42. 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 101:566-572, 2005
43. Lavand'homme PM, Roelants F, Waterloos H, et al: An evaluation of the postoperative antihyperalgesic and analgesic effects of intrathecal clonidine administered during elective cesarean delivery. Anesth Analg 107:948-955, 2008
44. Dadure C, Motais F, Ricard C, et al: Continuous peripheral nerve blocks at home for treatment of recurrent complex regional pain syndrome I in children. Anesthesiology 102:387-391, 2005
45. Kong VK, Irwin MG: Gabapentin: a multimodal perioperative drug? Br J Anaesth 99:775-786, 2007
46. Seib RK, Paul JE: Preoperative gabapentin for postoperative analgesia: a meta-analysis. Can J Anaesth 53:461-469, 2006

47. Ho KY, Gan TJ, Habib AS: Gabapentin and postoperative pain—a systematic review of randomized controlled trials. Pain 126:91-101, 2006
48. Hurley RW, Cohen SP, Williams KA, et al: The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med 31:237-247, 2006
49. Zhang J, Ho KY, Wang Y: Efficacy of pregabalin in acute postoperative pain: a meta-analysis. Br J Anaesth 106:454-462, 2011
50. Wilder-Smith CH, Hill LT, Laurent S: Postamputation pain and sensory changes in treatment-naive patients: characteristics and responses to treatment with tramadol, amitriptyline, and placebo. Anesthesiology 103:619-628, 2005
51. Dahl E, Cohen SP: Perineural injection of etanercept as a treatment for postamputation pain. Clin J Pain 24:172-175, 2008
52. Katayama Y, Yamamoto T, Kobayashi K, et al: Motor cortex stimulation for phantom limb pain: comprehensive therapy with spinal cord and thalamic stimulation. Stereotact Funct Neurosurg 77:159-162, 2001
53. Chan BL, Witt R, Charrow AP, et al: Mirror therapy for phantom limb pain. N Engl J Med 357:2206-2207, 2007
54. Tran de QH, Duong S, Bertini P, et al: Treatment of complex regional pain syndrome: areview of the evidence. Can J Anaesth 57:149-166, 2010
55. Kroin JS, Takatori M, Li J, et al: Upregulation of dorsal horn microglial cyclooxygenase-1 and neuronal cyclooxygenase-2 after thoracic deep muscle incisions in the rat. Anesth Analg 106:1288-1295, 2008