



Preventing chronic pain following acute pain: Risk factors, preventive strategies, and their efficacy

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ABSTRACT

Chronic pain is the leading cause of disability in the United States. The transition from acute to persistent pain is thought to arise from maladaptive neuroplastic mechanisms involving three intertwined processes, peripheral sensitization, central sensitization, and descending modulation. Strategies aimed at preventing persistent pain may target such processes. Models for studying preventive strategies include persistent post-surgical pain (PPP), persistent post-trauma pain (PTP) and post-herpetic neuralgia (PHN). Such entities allow a more defined acute onset of tissue injury after which study of the long-term effects is more easily examined. In this review, we examine the pathophysiology, epidemiology, risk factors, and treatment strategies for the prevention of chronic pain using these models. Both pharmacological and interventional approaches are described, as well as a discussion of preventive strategies on the horizon.

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1. Introduction

Up to 56 million American adults (28% of the adult population) experience chronic pain (Brennan et al., 2007). The annual cost of chronic pain in the United States, including healthcare expenses, lost income, and lost productivity, is estimated to be \$100 billion (National Institutes of Health. NIH guide: new directions in pain research: 1. Bethesda, MD: National Institutes of Health; 1998). According to the Centers for Disease Control and Prevention, chronic pain is the leading cause of disability in the United States.

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Maladaptive mechanisms may occur resulting in persistent pain despite removal of the inciting injury, commonly referred to as chronic pain. It is generally held that when pain persists beyond the expected timeframe for resolution and recovery from tissue injury, this constitutes the bridge from acute to chronic pain (Stubhaug, 2005).

Models for studying strategies for the prevention of chronic pain following acute pain include persistent post-surgical pain (PPP), persistent post-trauma pain (PTP), and post-herpetic neuralgia (PHN). Such entities allow a more defined acute onset of tissue injury after which study of the long-term effects is more easily

examined. In this review, we examine the pathophysiology, epidemiology, risk factors, and treatment strategies for the prevention of chronic pain using these models. First, a broad overview of pathophysiology of PPP, PTP and PHN is provided to highlight important areas for targeted interventions.

1.1. Etiology of persistent pain following surgery or trauma

The ability to detect noxious stimuli is a protective mechanism of most organisms and is essential for survival. An acute injury, as with surgery or trauma, leading to chronic pain is associated with neuroplastic changes in the peripheral and central nervous system in response to the nociceptive input. Such changes lead to nervous system hypersensitivity which, in turn, promotes guarding of the injured area. Persistence of these changes often leads to debilitating chronic pain. Three intertwined processes may serve as targets for the prevention of chronic pain, and include peripheral sensitization, central sensitization, and descending modulation, as illustrated in Fig. 1.

1.1.1. Peripheral sensitization

Peripheral nociceptors are activated when stimulus intensity reaches the noxious range. Acute pain may arise from damage to peripheral tissue and nerves, as with surgical or traumatic tissue injury, leading to increased spontaneous firing and alterations in the transduction, conduction or neurochemical sensitivity of nociceptive afferent fibers. A phenomenon known as neurogenic inflammation also occurs, whereby inflammatory products are released by activated nociceptors, leading to a cascade of events

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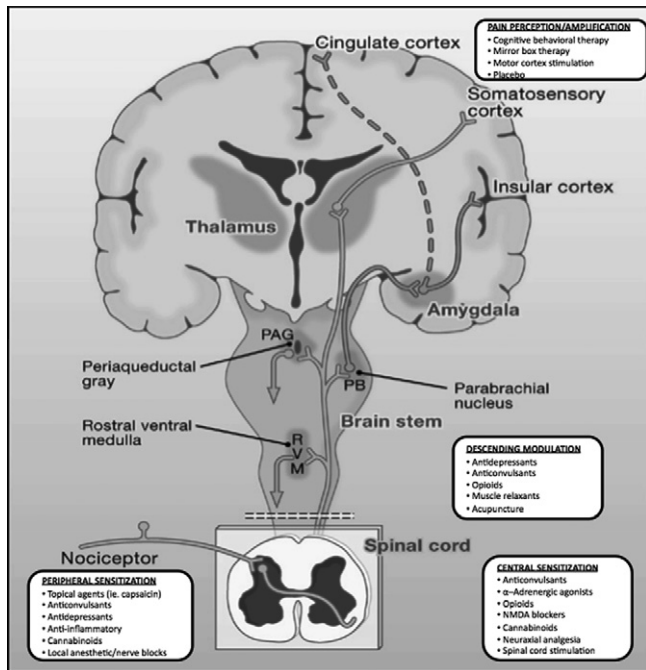


Fig. 1. Schematic representation of multifactorial nature of neuropathic pain. Potential targets include peripheral sensitization, central sensitization and descending modulation (adapted from Basbaum et al., 2009).

involving enhanced ion channel permeability, gene expression, and receptor and channel density on the cell membrane. The consequence of these events is peripheral nociceptor hyperexcitability, termed 'peripheral sensitization'. Anti-inflammatory medications are theorized to target inflammatory markers, thereby interfering with neurogenic inflammation, and suppressing peripheral sensitization. While an obvious target for investigation, prospective studies of anti-inflammatory medication for the prevention of chronic pain are lacking. Anticonvulsants, on the other hand, have been a target of intense research, as these membrane stabilizers share a common mechanism of sodium channel blockade, thus interfering with peripheral sensitization. Other treatments targeting peripheral sensitization include antidepressants, cannabinoids, local anesthetics, and topical agents, as illustrated in Fig. 1.

1.1.2. Central sensitization

Persistent excitability of peripheral afferents may extend to involve the dorsal horn or higher centers in the central nervous system. Enhanced activation of central synapses may result in N-methyl-D-aspartate (NMDA)-dependent mechanisms, such as central sensitization and long-term potentiation, whereby progressively less incoming stimulus is required to activate second and third order neurons. As with peripheral sensitization, cytokine, chemokines, and neuropeptides are implicated in the pathophysiology of central sensitization. This important phenomenon appears to be intimately associated with persistent pain following amputation. NMDA antagonists are theorized to provide a targeted treatment for the prevention of central sensitization and thus, chronic pain. The major clinical example is ketamine, although other NMDA antagonists have been investigated (e.g. memantine). The potential role of ketamine has been examined for the prevention of chronic pain following surgery, and is detailed later in this review. Opioids, α -adrenergic agonists, cannabinoids, neuraxial analgesia and spinal cord stimulation are also believed to play a role in altering central sensitization.

1.1.3. Descending modulation

The spinal dorsal horn, where multiple complex excitatory, inhibitory and modulatory mechanisms converge, serves as the interface between peripheral and central nociception. Interneurons, glial cells and descending inhibitory influences play an intricate role in pain modulation at the dorsal horn. It is also here that windup, central sensitization, and the resultant hyperalgesia and allodynia appear to be initiated. Animal studies and functional imaging studies in humans indicate that the duration of pain is determined, at least in part, by descending facilitatory mechanisms involving other structures such as the periaqueductal gray (PAG), rostral ventral medulla (RVM), and nucleus caudalis. Clinically, treatments that take advantage of subcortical supraspinal modulation include opioidergic, serotonergic and noradrenergic agonists (e.g. tramadol, tapentadol, and methadone), tricyclic antidepressants (TCA) (e.g. nortriptyline) and serotonin-norepinephrine reuptake inhibitors (SNRI) (e.g. duloxetine). Interestingly, even some anticonvulsants (e.g. gabapentin and pregabalin) have been shown to activate the descending noradrenergic system (Hayashida et al., 2007). While TCA and SNRI have yet to be examined carefully for the prevention of chronic pain, multiple studies on the long-term effects of gabapentinoids following surgery and amputation are critically reviewed later in this article.

Supraspinal processing and modulation of pain has more recently implicated higher centers, including thalamocortical connections, somatosensory cortices (SSC), anterior cingulate cortex (ACC), insula, motor cortex (MC), dorsolateral prefrontal cortex (DLPFC) (Fierro et al., 2010), orbitofrontal cortex (OFC) and amygdala (Moont et al., 2011), among others (Basbaum et al., 2009). Cognitive-behavioral therapy, biofeedback, distraction, mirror-box therapy (as utilized for phantom limb pain), motor cortex stimulation (Fierro et al., 2010) and the placebo effect are all recognized to impact supraspinal mechanisms involving these important regions.

1.2. Persistent post-surgical pain (PPP)

PPP is an important model for studying the transition from acute to chronic pain in humans, as there is a growing body of literature from basic and clinical investigation examining mechanistic features and therapeutic outcomes. Individuals who develop PPP experience pain that may be severe enough to interfere with work, sleep, mood, social life and overall quality of life, lending further support for this entity to serve as a platform for understanding persistent pain.

1.2.1. Definition

While there is no consensus on the exact definition for PPP, Macrae provided the following criteria: (1) pain that develops after surgery, (2) pain of at least two months' duration, and (3) other causes of pain have been excluded (Macrae, 2008). Others have defined it more simply as postoperative pain that persists for three to six months after surgery (Kehlet et al., 2006). Most would agree, however, that in addition to such criteria, a neuropathic quality of pain, often described as 'burning', 'shooting', or 'electric-like', should be ascertained in the clinical evaluation of a patient with suspected PPP. The presence of clinical signs of hyperalgesia or allodynia may be used to corroborate these findings. Additionally, as further research on the clinical detection of the transition from peripheral to central sensitization becomes available (e.g. diffuse noxious inhibitory control (DNIC) as a measure of identifying patients at risk (Yarnitsky et al., 2008), an accurate, reliable and unified definition may become available.

1.2.2. Epidemiology

There is evidence that PPP is more prevalent than traditionally accepted, though a wide range of incidences have been reported among various operations. The incidence of post-cesarean chronic pain has been reported as 12.3% (Nikolajsen et al., 2004), while 19% of patients met the IASP criteria for chronic pain 6 months following knee replacement (Stanos et al., 2001). Approximately 28% of patients undergoing elective inguinal herniorrhaphy reported chronic pain (Mikkelsen et al., 2004), and in a retrospective cohort study, 52% of patients undergoing mastectomy had persistent pain for 9 years (Macdonald et al., 2005). The incidence of chronic post-thoracotomy pain syndrome has been reported between 50% and 80% (Senturk et al., 2002). Such variability may be dependent on multiple factors, including surgical factors as described in the next section.

1.2.3. Risk factors and predictors of PPP

Not everyone experiences persistent pain following an acute injury. In PPP, this variability may be a function of a variety of factors throughout the preoperative, intraoperative and postoperative periods, as detailed in Fig. 2.

In the preoperative period, non-modifiable patient-related risk factors include age and gender. Older patients tend to have a lower risk of developing PPP than younger patients (Massaron et al.,

2007). Studies have shown that females are more likely than males to have PPP (Caumo et al., 2002). Modifiable risk factors include high body mass index (≥ 25) (Massaron et al., 2007), severe preoperative pain (Hanley et al., 2007), higher incidence of postoperative complications (Franneby et al., 2006), and the presence of chronic pain in other areas of the body (Lavand'homme, 2010). Additionally, psychological factors include anxiety, depression, post-traumatic stress disorder (PTSD, past life traumas (Casey et al., 2008) and catastrophizing (Peters et al., 2007). In particular, depression, psychological vulnerability, stress and duration of disability (time to return from work) are among the best psychosocial predictors of PPP (Hinrichs-Rocker et al., 2009). Additionally, genetic factors include polymorphisms of catechol-O-methyltransferase (COMT), genetic variants to determine voltage-gated sodium channels, GTP cyclohydrolase and tetrahydrobiopterin-related genes (Diatchenko et al., 2007), as well as those associated with impaired pain modulation (Diatchenko et al., 2005) have been described. Co-morbidities, including sleep disorders and other pain states, are also implicated. Environmental factors include the nature, intensity, and duration of pre-surgical pain (Peters et al., 2007; Bachiocco et al., 1990).

During the intraoperative and postoperative healing periods, important surgical factors include: the type of surgery, anatomical location of surgery, surgical technique, and the extent of nerve

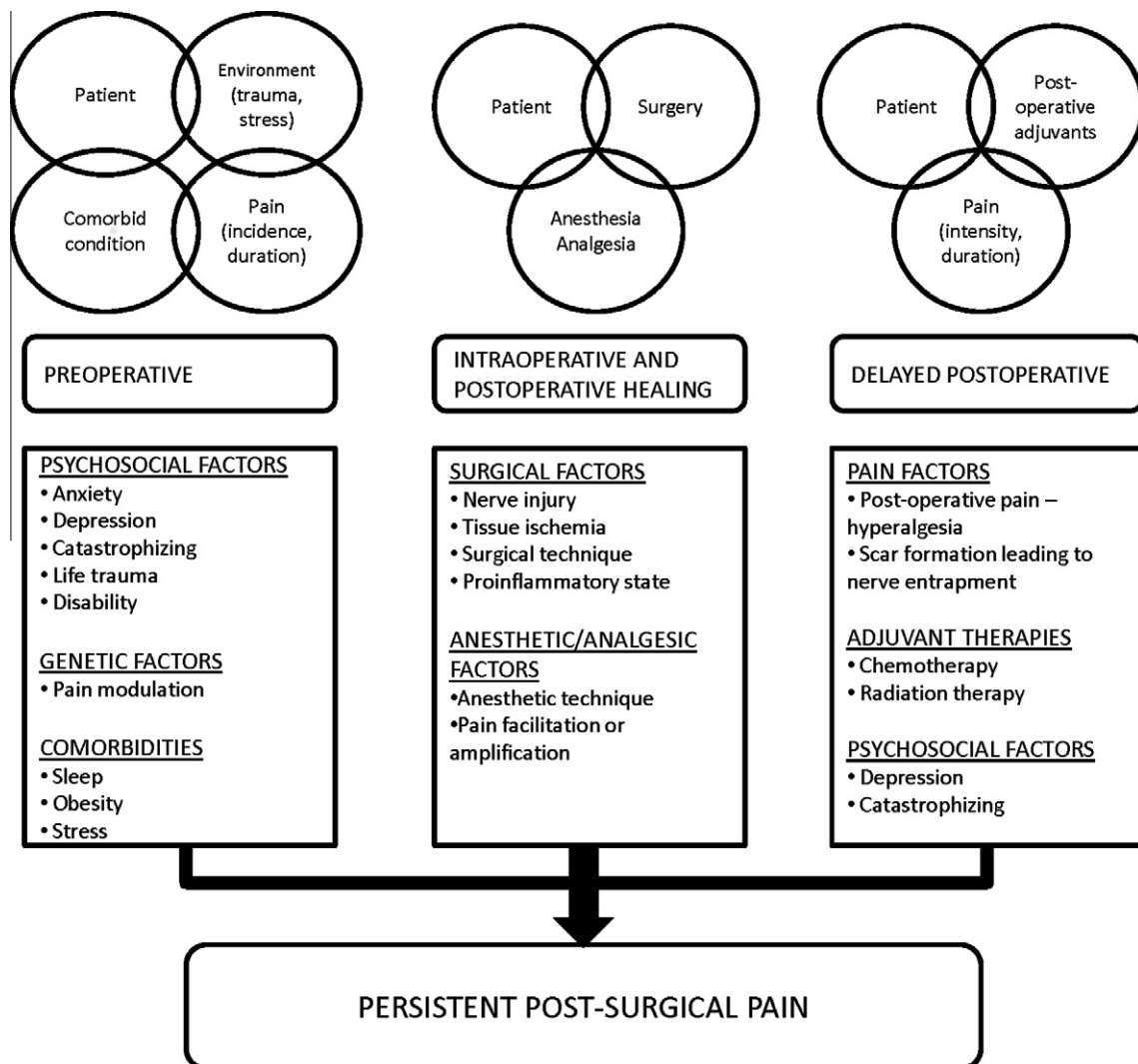


Fig. 2. Schematic illustrating risk factors for the development of chronic pain throughout the perioperative continuum (adapted from Wu and Raja, Lancet, 2011).

injury and tissue ischemia. For example, the degree of intercostal nerve injury is thought to be the primary determinant of persistent post-thoracotomy pain (Wildgaard et al., 2009). Specific surgeries have been associated with higher incidences of PPP, such as mastectomy, thoracotomy and inguinal herniorrhaphy. Efforts to optimize surgical techniques for such operations are an important area for research. For example, the incidence of chronic pain with significant impairment of daily activities was decreased from 42% of patients preoperatively to 8.3% after transabdominal preperitoneal patch plasty (Kehlet et al., 2010). Anesthetic and analgesic factors are also implicated during this period (Wildgaard et al., 2009).

In the delayed postoperative period, patient's psychosocial factors, adjuvant therapies, healing with scar formation, and pain control play critical roles. While surgical, anesthetic and analgesic factors are currently under scrutiny for prospective evaluations on the prevention of chronic pain, studies of the early treatment of patient-related psychosocial factors are lacking. Such interventions may include development and enhancement of coping skills, cognitive-behavioral therapy, biofeedback, and acupuncture, applied before and after surgery. This may serve as an important area for future investigation into the strategies of preventing chronic pain.

While a wide range of risk factors have been implicated in the development of PPP, no single factor appears to dominate. For example, less than 20% of the overall risk of chronic pain can be predicted by the severity of postoperative pain (Eisenach, 2006). However, it remains possible that the cumulative risk may become important in patients who have multiple risk factors. Further research is warranted to elucidate the benefit of risk stratification and appropriate treatment during the perioperative phases of surgery.

1.3. Persistent post-trauma pain (PTP)

Trauma, both civilian and military, remains a major source of morbidity and mortality throughout the world. Better body armor and improved evacuations have enabled modern age soldiers to survive blasts that would have been fatal in earlier decades. In addition, medical advances have significantly reduced the mortality associated with trauma, which has led to an increased emphasis on secondary outcome measures, such as psychological well-being, functional improvement, and vocational and social reintegration (Sinha, 2010). One of the new challenges for military medicine is how to deal with the pain of injuries to extremities that body armor cannot protect (Gallagher and Polomano, 2006).

1.3.1. Definition

PTP provides a prototypical model for studying the transition from acute to chronic pain. Many authors have found it useful to distinguish between residual limb pain (RLP), phantom sensation, and phantom limb pain (PLP). Pain in the residual limb is defined as pain at the site of an extremity amputation. Phantom sensation is defined as any sensation in the absent limb except pain. PLP is defined as painful sensations referred to the absent limb (Hill, 1999). For the purposes of this article, we will limit our discussion of post-trauma pain to PLP.

PLP has been described by patients as “stabbing” or “pins and needles”, although the pain experience can be unique to each amputee (Wartan et al., 1997). The onset of PLP may occur immediately following an amputation, with some occurring throughout the amputee's life. Although many individuals who have PLP report it as being mild and intermittent, it may be severe enough to interfere with a patient's work, sleep, and social life (Ketz, 2008).

1.3.2. Epidemiology

In a 2010 analysis, Barmparas et al. reviewed the National Trauma Databank version 5 to examine the epidemiology and outcomes of posttraumatic upper (UEA) and lower extremity amputations (LEA) (Barmparas et al., 2010). Of those with limb amputations, 92.7% had a single limb amputation. LEA was more frequent than UEA among patients in the single limb amputation group (58.9% vs 41.1%). The mechanism of injury was blunt in 83%; most commonly after motor vehicle collisions (51.0%), followed by machinery accidents (19.4%). Motor vehicle collision occupants had more UEA (54.5% vs 45.5%, $P < 0.001$), whereas motorcyclists (86.2% vs 13.8%, $P < 0.001$) and pedestrians (91.9% vs 8.1%, $P < 0.001$) had more LEA. Patients with LEA were more likely to require discharge to a skilled nursing facility; whereas those with UEA were more likely to be discharged home.

Estimates of the prevalence of phantom pain differ considerably in the literature, from 50% to 78% (Schley et al., 2008). This lack of agreement has occurred, in part, because prevalence rates for PLP have been derived from research studies in which the patient's request for treatment is the only indication of their pain status (Hill, 1999). Another reason may also be a function of the amputee's reluctance to report PLP to health care providers (Sherman et al., 1984).

1.3.3. Risk factors and predictors of PTP

Not all amputees experience persistent pain, and the reasons for this are unclear. Descriptive studies have identified factors that may contribute to the development of PLP: the degree of pre-amputation pain; the presence of noxious intraoperative inputs brought about by cutting skin, muscle, nerve, and bone; acute post-operative pain (including that due to pro-inflammatory processes); and psychological factors (Halbert et al., 2002; Parkes, 1973). One of the risk factors that seems to be associated with a higher prevalence of persistent pain is severe and poorly controlled pain before surgery, raising the possibility that providing good analgesia before amputation may well decrease the risk of developing chronic pain (Rathmell and Kehlet, 2011). Karanikolas et al. present the results of a small randomized, controlled trial (RCT) in patients undergoing amputation; the results further support the notion that providing for good pain control before amputation may minimize the risk of persistent pain after amputation (Karanikolas et al., 2011).

In their sample, nearly a third of amputees (28.7%) surveyed by Ephraim et al. were found to have depressive symptomatology. Amputees with pain were more likely to have depressive symptoms than those not experiencing pain. Likewise, depression was a key predictor of both reported intensity level and bothersomeness of chronic pain across all pain types after controlling for other factors. These results may support the need to assess the mood of persons reporting amputation-related pain and aggressively treat depression as part of the pain control program (Ephraim et al., 2005).

1.4. Post-herpetic neuralgia (PHN)

1.4.1. Definition

PHN is clinically defined as a chronic neuropathic pain condition characterized by allodynia or hyperalgesia in a dermatome(s) lasting at least 1–3 months following reactivation of varicella-zoster virus (VZV) in the dorsal root ganglia (DRG) of individuals having had a primary VZV infection. The natural history leading to PHN begins with symptoms arising from acute herpes zoster (HZ) infection, which includes numbness, itching and pain during the prodromal phase, followed by painful unilateral vesicular eruptions on the skin lasting for approximately 3–4 weeks (Opstelten et al., 2002). In approximately 20–25% of cases of HZ, painful

symptoms may persist for months or years after the vesicular lesions have healed (Schmader, 2002). PHN has been extensively studied and serves as a prototypical model for the study of neuropathic pain.

1.4.2. Epidemiology

The total lifetime risk of HZ has been reported to be approximately 25% (Miller et al., 1993) with the incidence almost doubling with every decade after the age of 50.5 (Donahue et al., 1995). This may be partly explained by a relative reduction of VZV-specific cell-mediated immunity as we age (Szucs et al., 2011). HZ affects more than 500,000 older adults in the US (Schmader et al., 2007). HZ results in significant morbidity, with the most severe complication being PHN. The incidence of PHN has been reported to be between 10% and 50% (Griffin et al., 1998; Stankus et al., 2000). PHN has been associated with significant impairment in quality of life, often leading to severe physical, occupational and social disabilities as a consequence of persistent pain.

1.4.3. Risk factors and predictors

Results of data analyses from a randomized, placebo-controlled trial of famciclovir indicated that greater age, rash severity, and acute pain severity were risk factors for prolonged PHN (Dworkin et al., 1998). Furthermore, univariate and multivariate analyses of 965 HZ patients enrolled within 72 h of rash onset in two clinical trials of famciclovir indicated that older age, female sex, presence of a viral prodrome, and greater severity of rash and acute pain were independent risk factors for the development of PHN (Jung et al., 2004).

1.5. General approaches to the prevention of PPP, PTP and PHN

Whenever possible, identifying and treating the underlying cause of nervous tissue injury is paramount. For example, early treatment of HZ with antiviral medication known to impair DNA replication of VZV virions may reduce the incidence of PHN. In addition, efforts to prevent or limit tissue injury should always

Table 1
Persistent post-surgical pain. Available evidence from prospective randomized controlled trials.

Author	Surgery	Study design	Route	Intervention	Results
Senturk et al. (2002)	Thoracotomy	RCT	Epidural	Bupivacaine and morphine: Pre-TEA: pre-op morphine 10 mL bolus of 0.1% bupivacaine and 0.1 mg/mL morphine at least 30 min prior to induction; intraop 7 mL/h infusion of same solution; post-op PCEA 0.1% bupivacaine and 0.05 mg/mL morphine (basal 5 mL/hr, bolus 3 mL, 30 min lockout); Post-TEA: without pre-TEA; PCA: 5 mg initial dose, no basal, 2 mg boluses with 15 min	Positive: the incidence of post-thoracotomy pain at 6 months in PCA group was significantly more frequent than in Pre-TEA ($P = 0.0233$)
De Kock et al. (2005)	Colonic resection	RCT	Intrathecal	Clonidine: 2 mL of intrathecal injection of 300 mcg of clonidine administered just prior to general anesthesia induction	Positive: statistically significant reductions in the area of hyperalgesia as measured by von Frey filament testing, and in the incidence of residual pain at 6 months
De Kock et al. (2001)	Colonic resection	RCT	Intravenous	Ketamine: subanesthetic high dose intravenous ketamine (0.5 mg/kg load then 0.25 mg/kg/hr infusion)	Positive: perioperative and persistent pain was significantly reduced when compared to low dose IV ketamine, epidural ketamine infusion and placebo. Approximately 30% of placebo subjects experienced persistent pain at 6 months, while no patients who received IV ketamine reported residual pain at the same time interval
Sen et al. (2009)	Hysterectomy	RCT	Oral	Gabapentin: 1200 mg per day; Ketamine: 0.3 mg/kg IV bolus and 0.05 mg/kg/h infusion until the end of surgery	Positive: the incidence and pain scores were significantly lower in the gabapentin group compared with the ketamine and control groups at 1, 3 and 6 months following elective hysterectomy
Tiippana et al. (2007)	Cesarean section	RCT	Oral	Gabapentin: 600 mg (single dose) 1 h before cesarean section (in addition to multimodal regimen of intrathecal fentanyl and morphine, oral acetaminophen and diclofenac, and systemic opioids for breakthrough pain)	Negative: no difference between groups in the incidence of persistent pain at 3 months post-operative
Brogly and Wattier (2008)	Thyroidectomy	RCT	Oral	Gabapentin: 1200 mg (single dose) 2 h preoperatively, as an adjunct to superficial cervical plexus block	Positive: the incidence and pain scores were significantly lower in the gabapentin group compared with placebo at 6 months following thyroidectomy
Fassoulaki et al. (2005)	Mastectomy	RCT	Oral	Gabapentin: 400 mg of gabapentin at every 6 h, starting the evening before surgery and continued until the eighth postoperative day; 20 g of EMLA cream applied from the day of surgery until the third postoperative day; Intraop irrigation of the brachial plexus block in the axilla with 10 mL of 0.75% ropivacaine and irrigation of the third, fourth, and fifth intercostal spaces with 3 mL of the same solution	Positive: multimodal analgesia with gabapentin and local anesthetics prevented acute and chronic pain after breast surgery for cancer
Buvanendran et al. (2010)	Total knee arthroplasty	RCT	Oral	Pregabalin: 300 mg 1–2 h before surgery, and for 14 days after surgery (150 mg twice daily for the first 10 postoperative days, 75 mg twice daily on Days 11 and 12, and 50 mg twice daily on Days 13 and 14)	Positive: reduction in both post-operative and chronic neuropathic pain following TKA. At both 3 and 6 months postoperatively, there was a statistically significant reduction in the incidence of neuropathic pain in the pregabalin group (0%) compared with the placebo group (8.7% and 5.2% at 3 and 6 mo, respectively)

be entertained. For example, careful dissection of tissue and the use of the least invasive surgical approach possible in addition to sustained multimodal pharmacological methods that target the underlying mechanisms of neuropathic pain are recommended (Kehlet et al., 2006).

Despite such efforts, 'chronification' of pain may still exist. Thus, several approaches to the prevention of chronic pain are described. *Primary prevention* of chronic pain refers to the prevention of acute pain (Stubhaug, 2005). Here, clinical models such as PPP and PHN can provide insight into preventive strategies (Peters et al., 2007). *Preemptive analgesia* is a form of primary prevention. The goal here is to prevent or interfere with mechanisms involved in peripheral or central sensitization. For example, sensitizing stimuli may be intraoperative and postoperative, therefore, in theory, treating during these phases of operative care are of significance. *Secondary prevention* refers to early identification and aggressive treatment of acute or subacute pain, thereby preventing chronic pain (Stubhaug, 2005). The goal is intervention to prevent central sensitization even if peripheral sensitization has already occurred. *Multimodal analgesia* is an approach involving the combination of opioid and non-opioid analgesics that act at different sites within the pain pathway construct, have additive or synergistic effects, and improve pain control, while eliminating opioid-related side effects (Rasmussen et al., 2010; Hong et al., 2010; Ong et al., 2010; Bisgaard, 2006; Kjetil et al., 2007; Kim et al., 2011; Trabulsi et al., 2010; Chen et al., 1998).

1.6. Evidence-based review of preventive strategies for PPP, PTP and PHN

Preventive strategies for PPP often utilize principles of primary and secondary prevention, including preemptive and multimodal approaches. Multimodal analgesia, which includes targeted pharmacological therapies with varying mechanisms of action using a combination of delivery routes (i.e. enteral, parenteral, epidural,

intrathecal) administered at variable time points (i.e. preoperative, intraoperative, and postoperative), is used to optimize outcomes in the treatment of acute pain and prevention of chronic pain. Such evidence-based analgesic strategies are described in detail, and illustrated in Tables 1 and 2.

1.6.1. Epidural analgesia utilizing opioids and local anesthetics

Neuraxial analgesia, involving opioids and local anesthetics, is often used in perioperative medicine. Animal research has shown that pre-injury treatment with local anesthetics or opioids can prevent spinal post-injury hyperexcitability. Two classes of local anesthetics, aminoamide and aminoester, are used in perioperative management, and share the common mechanism of action of sodium channel blockade. Opioids bind to various receptors including mu-opioid receptors, which are found in multiple regions of the neuraxis including the PAG and the dorsal horn. As detailed earlier (Fig. 1), both regions are thought to serve as important sites for the descending modulation of pain, and hence, serve as excellent targets for the prevention of central sensitization and chronic pain. More recently, studies point to the beneficial effect of optimizing perioperative analgesia with the combination of opioids and local anesthetics for the prevention of chronic pain.

Preoperative opioid analgesics have been shown to reduce postoperative pain, secondary hyperalgesia, and oral opioid requirements. Intravenous morphine (Richmond et al., 1993; Katz et al., 2003; Senturk et al., 2002), epidural fentanyl and epidural morphine have been used in this setting. The incidence and intensity of pain in the group receiving epidural morphine pre-, intra-, and post-operatively had significantly less pain than in the IV morphine PCA group (Table 1). No significant difference was found between the pre-thoracic epidural group and post-thoracic epidural group (Senturk et al., 2002). This study as well as previous studies have indicated a predictive relationship between post-thoractomy acute pain and persistent pain, though limited by small sample size (Katz et al., 2003; Senturk et al., 2002), and suggest that preopera-

Table 2
Persistent post-trauma pain. Available evidence from prospective randomized controlled trials.

Author	Surgery	Study design	Route	Intervention	Results
Karanikolas et al. (2011)	Limb amputation	RCT	Epidural	Bupivacaine and fentanyl: Epi/Epi/Epi vs PCA/Epi/Epi vs PCA/Epi/PCA vs PCA/GA/PCA vs Control. Epidural: bupivacaine 2 mg/ml, and fentanyl 2 mcg/ml, infusion at 4–8 ml/h, starting 48 h before, continuing until 48 h after amputation. PCA: fentanyl PCA dose, 25 mcg; lockout, 20 min; and no basal	Positive: significant reduction in prevalence and intensity of phantom-limb pain in all treatment groups at 6 months post-operative on VAS and MPQ No significant difference between treatment groups
Jahangiri et al. (1994)	Limb amputation	RCT	Epidural	Bupivacaine, morphine and clonidine: pre-, intra- and post-operative epidural bupivacaine, morphine, and clonidine	Positive: epidural analgesia provided significantly less PLP at 1 year than those who received postoperative opioids only ($P < .002$)
Bach et al. (1988)	Limb amputation	RCT	Epidural	Bupivacaine and morphine: preoperative lumbar epidural blockade (LEB) 72 hrs before surgery	Positive: LEB group was pain-free after 6 months and 1 year vs control group ($P < 0.05$)
Nikolajsen and Ilkjaer (1997)	Limb amputation	RCT	Epidural	Bupivacaine and morphine: pre- and peri-operative epidural bupivacaine and morphine delivered 1 h prior to surgery	Negative: epidural analgesia delivered 18 h prior to surgery did not prevent acute or chronic PLP
Lambert et al. (2001)	Limb amputation	RCT	Epidural regional	Bupivacaine and Diamorphine: epidural bupivacaine 0.166%, 2–8 mL/h and diamorphine 0.2–0.8 mg/h for 24 h before and during operation and 3 days postoperatively; intra- and post-operative perineural bupivacaine 0.25%, 10 mL/h	Negative: epidural analgesia started 24 h before amputation is not superior to infusion of local anaesthetic via a perineural catheter in preventing phantom pain, but gives better relief of stump pain in the immediate postoperative period
Nikolajsen et al. (2006)	Limb amputation	RCT	Oral	Gabapentin: gradual titration to 2400 mg/day over 30 days post-operative	Negative: gabapentin administered in the first 30 postoperative days after amputation does not reduce the incidence or intensity of post-amputation pain
Nikolajsen et al. (2000)	Limb amputation	RCT	Oral	Memantine: gradual titration to 20 mg/day over 5 weeks post-operative	Negative: memantine administered in the first 5 weeks after amputation does not reduce spontaneous or evoked post-surgical/amputation pain

tive epidural analgesia may be an important preventive strategy for post-thoracotomy chronic pain. Further investigations reproducing these results are warranted.

Prior studies on the prevention of post-amputation pain have provided conflicting results (Nikolajsen and Ilkjaer, 1997; Nikolajsen et al., 2006; Table 2). In a recent RCT evaluating patients undergoing lower limb amputation for non-traumatic disease, statistically significant reductions in PLP prevalence and intensity at 6 months were identified in subjects receiving a combination of epidural and intravenous analgesia during the pre-, intra-, and postoperative periods when compared to a control. There were no significant differences between the treatment groups, although a trend was noted in favor of the group receiving epidural analgesia throughout each phase of the perioperative period (Karanikolas et al., 2011). Patients who received pre-, intra- and post-operative epidural bupivacaine, diamorphine, and clonidine had significantly less PLP at 1 year than those who received postoperative opioids only ($P < .002$) (Jahangiri et al., 1994). Conversely, a randomized, double-blind trial showed epidural bupivacaine and morphine administered 18 h pre- and intra-operatively did not prevent acute or chronic PLP (Nikolajsen and Ilkjaer, 1997). Lambert et al. compared post-amputation pain in patients randomly assigned to receive either epidural bupivacaine and diamorphine from 24 h preoperatively to 3 days postoperatively, or perineural bupivacaine peri- and post-operatively. There was no significant advantage with preoperative epidural bupivacaine and diamorphine in the prevention of PLP, although it did relieve acute RLP significantly (Lambert et al., 2001). A cross-sectional survey comparing pain interviews 1 week to 14 months after amputation showed no significant difference in chronic pain among those who received spinal, epidural, or general anesthesia. Interestingly, patients who received epidural or spinal anesthesia reported significantly less acute pain than those who received general anesthesia, but there was no difference between the three groups in the postoperative use of pain medication (Ong et al., 2006). Given the potential link between pre-amputation and acute pain and chronic PLP, further studies are warranted to determine ways to prevent early pain in high-risk patients.

Multiple studies investigating the role of local anesthetics through various routes for acute postoperative pain have consistently shown benefit, however, many of these studies did not specifically set out to investigate longer term effects on the development of chronic pain (Grainier et al., 2009; Perinola et al., 2009; Kaba et al., 2007; Lauwick et al., 2008; Lavand'homme et al., 2005). It may be theorized that aggressive management of acute pain through primary and secondary prevention strategies may reduce the development of central sensitization and chronic pain. However, further studies are warranted to substantiate or refute this claim.

The benefits of epidural local anesthetics are not restricted to surgical patients. Since acute HZ infection involves a robust inflammatory response in the vicinity of the DRG, epidural steroid injection (ESI) or infusion would appear to be a rationale approach to early treatment and prevention of PHN. Pasqualucci et al. was able to show that epidural administration of local anesthetic and methylprednisolone was significantly more effective in preventing PHN at 1, 3, 6, and 12 months when compared to intravenous acyclovir and prednisolone (Pasqualucci et al., 2000). Optimum pain relief with continuous epidural infusion of local anesthetics shortens the duration of zoster-associated pain (Dworkin and Portenoy, 1996; Manabe et al., 2004). However, the evidence for neuraxial analgesia utilizing local anesthetic and steroid for the prevention of PHN has been conflicting. While single epidural injection of steroids and local anesthetics in the acute phase of HZ had a modest effect in reducing zoster-associated pain for 1 month; it was not effective for prevention of long-term PHN (van Wijck et al.,

2006). Based on a systematic review of neuraxial blocks in HZ and PHN, strong evidence for the beneficial effect of either epidural or intrathecal administration of local anesthetic and steroid during acute HZ was presented. If given within 2 months of acute HZ infection, epidural local anesthetic and steroid may reduce the incidence of PHN after 1 year (grade A). Evidence for use of sympathetic blocks in HZ and PHN, although generally useful (Grade B) requires RCTs for validation. Levels of evidence and grades of recommendation varied among these studies and should be taken into consideration (Kumar et al., 2004).

1.6.2. Neuraxial analgesia utilizing clonidine

The alpha-2-adrenergic agonist, clonidine, delivered intrathecally, has been utilized as a unique adjuvant for perioperative pain management. The mechanisms underlying this anti-nociceptive effect are likely to be multifactorial, and involve inhibitory effects on hyperalgesic neurons at the level of the dorsal horn through gamma aminobutyric acid (GABA) properties, as well as activation of descending inhibitory pathways, mimicking the effect of endogenous norepinephrine in the descending modulation of pain (see Fig. 1). Randomized, placebo controlled studies have shown a reduction in the incidence of chronic pain at 6 months in patients receiving intrathecal clonidine prior to surgery (Eisenach et al., 2008; De Kock et al., 2005). Two mL of intrathecal injection of 300 mcg of clonidine was administered just prior to general anesthesia induction to patients undergoing surgical resection of colon adenocarcinoma, and offered statistically significant reductions in the area of hyperalgesia as measured by von Frey filament testing (Perkins and Kehlet, 2000), and in the incidence of residual pain at 6 months. This study highlights the beneficial analgesic effects of alpha-2 agonism on secondary hyperalgesia and its potential as an agent in preventing central sensitization and PPP (De Kock et al., 2005). Further studies are warranted to reproduce and substantiate these findings.

1.6.3. Adjuvant non-opioid treatments

1.6.3.1. *Anticonvulsants.* The gabapentinoids have been a mainstay of treatment for chronic neuropathic pain based on multiple RCTs in patients with post-herpetic neuralgia (PHN) and painful diabetic peripheral neuropathy (PDPN) (Rowbotham et al., 1998; Rice and Maton, 2001; Gilron et al., 2009; Gilron et al., 2005; Backonja et al., 1998; Serpell, 2002; Freynhagen et al., 2005; Lesser et al., 2004; Dworkin et al., 2003). The mechanisms of action of gabapentin or pregabalin involve binding to presynaptic alpha-2-delta subunit of N-type voltage-gated calcium channels (VGCC) in the dorsal root ganglia, which ultimately reduces calcium-dependent release of excitatory neurotransmitters such as glutamate, noradrenaline, calcitonin-gene-related-peptide (CGRP), and substance P (SP). In addition, gabapentin has been shown to exert modulatory effects at the level of the PAG (Morgado et al., 2010). These serve as important areas for the development of peripheral sensitization, central sensitization and chronic pain, and may provide targets for the prevention of PPP.

Studies have shown benefit with perioperative gabapentin for various surgical procedures including hysterectomy (Fassoulaki et al., 2006; Sen et al., 2009), thyroidectomy (Brogly and Wattier, 2008), and mastectomy (Fassoulaki et al., 2005) (Table 1). Findings in these studies were more profound than described in other studies of gabapentin for prevention of chronic pain (Tiippana et al., 2007), although a more robust response may be partially explained by more aggressive dosing of gabapentin. The optimal dosing, timing and frequency of perioperative gabapentin remains unclear. Such discrepancies in the results of various studies underscore the challenges behind study design. With regard to PTP, a study that used gabapentin in the postoperative phase found no significant preventive effect (Nikolajsen et al., 2006).

Pregabalin, when administered before surgery, and for 14 days after surgery, resulted in a reduction in both postoperative and chronic neuropathic pain following total knee arthroscopy (TKA). At both 3 and 6 months postoperatively, there was a statistically significant reduction in the incidence of neuropathic pain in the pregabalin group (0%) compared with the placebo group (8.7% and 5.2% at 3 and 6 mo, respectively), as measured by Leeds Assessment of Neuropathic Symptoms and Signs scale. Patients receiving pregabalin also had statistically significant reductions in epidural opioids, oral opioid pain medication while hospitalized, and had greater active flexion over the first 30 postoperative days (Buvanendran et al., 2010).

Carbamazepine was previously the most commonly used anti-convulsant, and has been used as first-line therapy for neuropathic pain conditions such as trigeminal neuralgia. Elliott et al and Patterson reported cases of lancinating PLP that improved with oral carbamazepine, but there is no evidence that it is effective for pain not described as intermittent, intense, and of lancinating quality (Elliott et al., 1976; Patterson, 1988). Other membrane stabilizers have not been extensively studied for the purpose of preventing chronic pain.

Multiple studies investigating the role of anticonvulsants for acute postoperative pain have consistently shown benefit; however, many of these studies did not specifically set out to investigate longer term effects on the development of chronic pain (Kim et al., 2011; Rasmussen et al., 2010). Again, aggressive management of acute pain through primary and secondary prevention may reduce the development of central sensitization and chronic pain. However, studies are warranted to substantiate or refute this claim. Additionally, while several RCTs validate the use of anticonvulsants for the treatment of PHN, high-quality investigations of anticonvulsants for the prevention of PHN are warranted.

1.6.3.2. Antidepressants. Both TCA and SNRI have been frequently used in the treatment of chronic neuropathic pain states such as painful diabetic peripheral neuropathy and post-herpetic neuralgia (Gilron et al., 2009; Watson and Babul, 1998; Raskin et al., 2005; Wernicke et al., 2006; Goldstein et al., 2005). In the case of PLP, amitriptyline is effective in patients who have never received analgesic treatment or have no relief with tramadol (Wilder-Smith et al., 2005). Their impact on descending modulation of pain provides an ideal target for the prevention of chronic pain (Fig. 1). Additionally, given that anxiety and depression is present in 30–65% of patients with chronic pain, such conditions may play a role in durability of pain. Therefore, treatments with antidepressant effects may be beneficial. It is unclear if early treatment following nervous system injury is protective against the persistence of pain, however. Further prospective investigations are warranted. Bowsher suggested, based on a small randomized trial, that pre-emptive treatment with low-dose tricyclic antidepressants (TCAs; ami- or nor-triptyline 10–25 mg at bed time) from the time of diagnosis of acute shingles reduces the incidence of postherpetic neuralgia by about 50% (Bowsher, 1997). Bowsher also retrospectively reviewed features of postherpetic neuralgia (PHN) in up to 279 patients treated with TCAs (Bowsher, 2003) and concluded that a critical factor was the point in time at which TCA treatment was commenced. When started between 3 and 12 months after acute zoster onset, more than two-thirds obtained pain relief; between 13 and 24 months, two-fifths (41%); and more than two years, one-third. The potential role of antidepressants in preventing PHN needs further careful prospective studies.

1.6.3.3. Lidocaine patch. Multiple studies investigating the role of 5% lidoderm patch for neuropathic pain associated with PHN have consistently shown benefit; however, many of these studies did not specifically set out to investigate preventive effects on the

development of PHN following acute HZ infection (Davies and Galer, 2004).

1.6.3.4. Anti-inflammatory drugs. As previously discussed, neurogenic inflammation is a major propagating event in the transmission of pain in both the peripheral and central nervous system. The important question is whether aggressive prevention and treatment of acute pain with anti-inflammatory medications limit the progression of sensitization and chronic pain. While multiple studies investigating the role of non-steroidal anti-inflammatory drugs (NSAIDs) and steroids for acute postoperative pain have consistently shown benefit, many of these studies did not specifically set out to investigate longer term effects on the development of chronic pain (Bisgaard, 2006; White et al., 2007; Gan et al., 2004; Hong et al., 2010; Ong et al., 2010; Kjetil et al., 2007). A systematic review concluded that corticosteroids given acutely during HZ infection are ineffective in preventing PHN. However, corticosteroids have been recommended to relieve the zoster-associated pain in the acute phase of disease (Chen et al., 2010). Aggressive management of acute pain through primary and secondary prevention may reduce the development of central sensitization and chronic pain, however, high quality studies with long-term follow-up are warranted to substantiate or refute this claim.

1.6.3.5. NMDA antagonists. NMDA antagonists have been shown to reduce central sensitization and generally act on the central nervous system. The best studied NMDA antagonist for pain is ketamine. In a randomized placebo controlled trial of subanesthetic high dose intravenous ketamine (0.5 mg/kg load then 0.25 mg/kg/hr infusion), perioperative and persistent pain was significantly reduced when compared to low dose IV ketamine, epidural ketamine infusion and placebo. Approximately 30% of placebo subjects experienced persistent pain at 6 months, while no patients who received IV ketamine reported residual pain at the same time interval (De Kock et al., 2001). Additionally, ketamine has been shown to reduce opioid consumption in the perioperative period, and by virtue of reduction in postoperative pain and opioid requirements, this may reduce the risk for persistent pain following surgery (Lavand'homme et al., 2005). The effectiveness of ketamine for prevention of PLP was studied in a prospective, observational study with historical controls with 14 patients in each group. The study showed that PLP remained as high as 72%. However, only 9% of the patients complained of severe PLP after ketamine compared to 71% of the patients in the control group (Dertwinkel et al., 2002). Further prospective studies are warranted to investigate aggressive intervention in the perioperative period and the incidence of subacute to chronic pain.

A study that used the NMDA receptor antagonist memantine versus placebo in addition to brachial plexus anesthesia in patients undergoing traumatic amputations of individual fingers or a hand found a reduction of PLP. However, its long-term effects were not clear (Schley et al., 2007). Other studies using solely memantine failed to show any benefit. (Schley et al., 2007; Maier et al., 2003).

1.6.3.6. Beta blockers. Beta-adrenergic blockers cause dilation of peripheral blood vessels and have been suggested for treatment of PLP based on a three-case series that showed improvement, though the exact mechanism is unknown (Marsland et al., 1982). However, a double-blind cross-over trial of propranolol (up to 240 mg daily), showed no significant improvement in PTP (Scadding et al., 1982). Further investigation into the role of beta-blockers for the prevention of chronic pain is warranted.

1.6.3.7. Vaccination. VZV vaccination, a form of primary prevention, reduces the incidence of HZ and PHN (Oxman and Levin, 2008). A

cost-effectiveness model of a live-attenuated vaccine aimed at preventing HZ and PHN predicted clinical and economic benefits of vaccination in the form of fewer HZ and PHN cases and reductions in healthcare resource use (Szucs et al., 2011). However, direct evidence from high quality clinical trials was insufficient to prove the efficacy of vaccine for preventing PHN beyond its effect on reducing HZ, although vaccination may be efficacious and safe for preventing HZ, thereby reducing the incidence of PHN in adults aged 60 years or older (Chen et al., 2011).

1.6.3.8. Antiviral medications. According to a Cochrane Review on antiviral treatment for preventing PHN, meta-analysis of multiple prospective studies including RCTs have consistently shown that while the incidence of PHN in patients receiving acyclovir was significantly different from those receiving placebo at 1 month after the onset of herpetic rash, there was no significant difference between the groups at 4 and 6 months (Li et al., 2009). However, only one trial was rated as good quality, while the others were rated as fair quality studies, limited by potential biases in the review process. While the action of acyclovir in preventing PHN is modest, prospective evaluation of newer antivirals such as famciclovir and valacyclovir show promise. The analyses by Dworkin et al. examined the effect of famciclovir on the duration of PHN, which was defined as pain persisting after rash healing, pain persisting >30 days after study enrollment, or pain persisting >3 months after study enrollment, and the prevalence of PHN at monthly intervals from 1 to 6 months after enrollment. They demonstrated that treatment of acute HZ patients with famciclovir significantly reduced both the duration and prevalence of PHN (Dworkin et al., 1998). A recent open-label study found that among 133 patients enrolled with acute HZ infection, the overall incidence of PHN was reduced to 9.8% at 6 months following acute combination treatment with gabapentin and valacyclovir; however, shortcomings included an open-label, uncontrolled study design. Furthermore, the optimal duration of antiviral treatment is unclear based on the available literature.

1.6.4. Preventive strategies on the horizon

Potential strategies that have been explored, but currently lack long-term investigations for the prevention of PPP, PTP and PHN include the use of acetaminophen, NSAIDs (e.g. ketorolac, celecoxib, ibuprofen), TCA, SNRI, opioids (oral, intravenous and transdermal), alpha-2 agonists (e.g. clonidine, dexmedetomidine), NMDA antagonists (e.g. memantine), regional anesthetic techniques using peripheral nerve catheters, interventional pain management (e.g. sympathetic block, spinal cord stimulation), continuous infusion of local anesthetics, genetics-based pain therapies (Wu and Raja, 2011), aggressive physical medicine and rehabilitation, pain psychology (e.g. cognitive-behavioral therapy, electromyographic feedback, hypnosis, and coping strategies), transcutaneous electrical nerve stimulation (TENS), complementary and alternative (CAM) modalities (e.g. acupuncture), imagery, mirrors, and even virtual reality treatment. Prospective RCTs evaluating such strategies are warranted in order to expand the armamentarium currently available for the prevention of chronic pain, as well as to better define important mechanisms responsive to treatment. Additionally, careful selection of patient populations under study cannot be overstated, and specific syndromes with a propensity toward the development of PPP and PTP should be entertained.

2. Discussion

We present a review of the pathophysiology, epidemiology, risk factors, and the available evidence of targeted treatment strategies

for the prevention of chronic pain using three prototypical models, PPP, PTP and PHN. The basis for choosing these pathologies includes the fact that a well defined acute onset of injury may be identified after which study of the long-term effects is more easily examined. Acute nervous tissue injury, as with surgery, trauma, or infection, leading to chronic pain, is associated with neuroplastic changes in the peripheral and central nervous system in response to the nociceptive input. Regardless of the inciting injury, three intertwined processes are implicated in the transition from acute to chronic pain, and include peripheral sensitization, central sensitization, and descending modulation. Risk factor modifications, and treatments, both pharmacological and interventional, may effectively target these processes for the prevention of chronic pain.

Randomized, controlled clinical trials (RCT) are believed to be the strongest clinical study design and are usually well accepted in today's evidence-based practices, although varying quality of such studies are possible. The strength of such studies is often dependent on several factors including adequate sampling, degree of internal validity, double blinding, and optimal selection of subjects, control group, and outcome measures as corroborated by IMMPACT recommendations (Dworkin et al., 2010). Systematic reviews of RCTs have also been utilized.

Based on the available evidence, neuraxial analgesia and gabapentinoids provide promising preventive effects for PPP, PTP and PHN. However, it would appear that PTP is more difficult to prevent than PPP or PHN, as illustrated in Tables 1 and 2. One possibility may relate to the degree of central nervous system changes, such that with PTP (PLP), a larger area of somatic tissue is compromised with amputation of an entire limb, corresponding to a larger area of somatotopic representation, with ensuing cortical reorganization that leads to central pain. Studies have consistently shown that central pain syndromes, including PLP, are among the most challenging to manage. As corroborated by the available evidence on the prevention of PPP, NMDA antagonism with ketamine for the prevention of PTP may serve as an important area of investigation from both a mechanistic and therapeutic standpoint, especially in light of the preponderance toward central changes in PTP.

Extrapolating from the available evidence on chronic pain and indirect study of acute pain, the following recommendations are provided: (1) aggressively optimize analgesia in the acute injury and pre-operative phase with extension into the post-operative/healing period, (2) screen patients for the presence of major depression and other psychiatric conditions with aggressive treatment concomitant to analgesic strategies, (3) identify patients who have modifiable risk factors for the development of chronic pain and manage accordingly, and (4) identify patients who have suboptimal responses during acute and subacute phases of treatment that are likely to develop chronic pain, so that comprehensive and interdisciplinary pain management can be initiated.

While a paucity of evidence-based strategies remains, many areas for future research are highlighted. The challenges we face when treating acute and chronic pain may not only be an issue of what we use to treat, but rather how and when we implement such treatments. Many basic questions remain: (1) When does central sensitization begin following tissue injury? (2) How do we detect the onset of central sensitization? (3) Are treatments provided too late in the disease course after central sensitization has already occurred? (4) Are currently available treatments ineffective or lacking potency despite early aggressive treatment as with preemptive, primary and secondary prevention? (5) Should treatments be maintained for longer periods of time, extending beyond initial nervous tissue injury? Further prospective studies are warranted to address these important questions.

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