Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage”\(^1\). It reflects a complex constellation of evolving effects at peripheral, spinal and cerebral levels involving several neurotransmitters and modulators and includes the immune system. Normally, acute surgical pain in most patients declines over the first few days after surgery, allowing them to recover uneventfully and to resume their normal daily activities within weeks.

Unfortunately, in a proportion of patients the pain can persist and become both chronic and severe\(^2\). Pain that persists after the surgical wound has healed could be the result of somatic nociception, the consequence of ongoing inflammation (e.g. infection, haematoma), a manifestation of neuropathic pain from surgical injury to peripheral nerves (e.g. complex regional pain syndromes, neuralgias)\(^3\), or from visceral nociception\(^2\). The International Association for the Study of Pain originally defined neuropathic pain as “pain due to a primary lesion or dysfunction of the peripheral or central nervous system”\(^4\). Post-traumatic neuropathic pain may affect nerve roots, peripheral nerves and the plexi or central neural structures. The clinical picture is dominated by both spontaneous resting and movement-provoked pain at both the site of surgery and the surrounding tissues, as well as pain distant from the surgical site (such as phantom pain)\(^3\).

The aims of this narrative review are to describe those factors in the perioperative pain experience that are predictive of the transition from acute perioperative to chronic post surgical pain, to explore the mechanisms involved and to propose preventive (or limitation) strategies and improved research designs.

METHODS

The review is based on an extensive search of the literature in relation to the topics covered without strict inclusion or exclusion criteria in the search strategy.

DEFINITION AND INCIDENCE

There is no definition of chronic post surgical pain that distinguishes it mechanistically from acute pain. The definition for chronicity relates to time periods only, which has ranged from one month to one year after surgery\(^5\), but in general has been defined as “pathological pain that persists for longer than two months post surgery”\(^6\).

Severe persistent (or chronic) post surgical pain may occur in 2 to 10% of surgical patients\(^7\). This discomfort generally lasts longer than six months after surgery\(^7\). In the United Kingdom, surgery is the second most common reason patients give for having developed chronic neuropathic pain\(^8\). Chronic pain of moderate to severe intensity occurs in 19% of adult Europeans\(^8\), which underscores the significance of the problem in the surgical population.

Some examples of the estimated incidence of chronic postoperative pain and disability after selected surgical procedures are given in Table 1.

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Accepted for publication on May 29, 2011.
MECHANISMS OF TRANSITION FROM ACUTE TO CHRONIC POST SURGICAL PAIN

Progression from acute to chronic pain involves altered pain processing. Postoperative pain is an association of somatic, inflammatory, neuropathic and visceral pain. Postoperative pain is a potent trigger for the stress response; it activates the central nervous system and is thought to be an indirect cause of adverse effects on various organ systems. Long-term neurobiological changes occur more quickly than previously anticipated within hours of acute injury.

Postoperative pain results not only from local tissue injury, leading to spontaneous firing of nociceptors and their increased sensitivity to stimuli (primary hyperalgesia), but also from central nervous system changes resulting in sensitisation and pain from a wider area (secondary hyperalgesia). Pain is not simply a reflection of peripheral inputs or pathology; it is also a dynamic reflection of central neuronal plasticity. The central neuronal plasticity profoundly alters sensitivity to an extent that it becomes a major contributor to many clinical pain syndromes; it represents a major target for therapeutic intervention. Secondary hyperalgesia is thought to be a basis for chronic post surgical pain. In addition, secondary hyperalgesia has many features or mechanisms related to memory at supraspinal sites.

The intraoperative injury barrage caused by nerve damage sensitises nociceptors in the surgical field, creating ectopic activity in sprouts of injured primary afferents and in somata of intact neurones in neighbouring dorsal root ganglia. Collateral sprouting occurs from neighbouring intact A delta afferents as well. During the process of regeneration of nerves, axonal sprouts generate neuronal activity that becomes most marked when neuromas develop. The consequent barrage of activity to the spinal cord leads to central sensitisation (hyperpathia, allosthenia and secondary hyperalgesia) that is a feature of neuropathic pain. Perioperatively, inadequate analgesia, extensive surgery, infection or increased peripheral ectopic activity from neuroma formation favours the development of central sensitisation.

Continued input from the perioperative noxious injury barrage maintains central sensitisation and secondary hyperalgesia, amplifies postoperative pain and contributes to chronic pain. Antinociceptive inhibitory interneurons in the dorsal horn disappear and result in centralisation of pain and somatosensory memories. However, most of the primary analgesics used to alleviate postoperative pain have only minor effects on secondary hyperalgesia. In addition, chronic post surgical pain may be part of a hypervigilant disease initiated in a vulnerable population by the preoperative stress or by the surgery itself. Precise distinctions between physiological and pathological contributions remain unclear.

Recently, a mechanism of neuronal plasticity in primary afferent nociceptive nerve fibres (nociceptors) has been identified by which an acute inflammatory insult or environmental stressor can trigger long-lasting hypersensitivity of nociceptors to inflammatory cytokines.

Hyperalgesic priming depends on the epsilon isoform of protein kinase C (PKC epsilon) and a switch in intracellular signaling pathways that mediate cytokine-induced nociceptor hyperexcitability. Studies in the rat model confirm a switch to a G(j)-activated and PKC epsilon-dependent signaling pathway in primary mechanical hyperalgesia that is induced by stress or inflammation. In the rat model, prostaglandin E (2) induced hyperalgesia is short-lived in naive rats, while it is prolonged in psepsilonRACK pre-treated (or primed) rats. Hyperalgesic priming occurs only in isolectin B4 (+) nociceptors. In the peripheral terminals of nociceptors, separate intracellular pools of PKC epsilon mediate nociceptor sensitisation, and the induction of hyperalgesic priming.

There is a suggestion that at least two downstream signaling pathways mediate the hyperalgesia induced by activating PKC epsilon. Inhibitors of two closely related mitochondrial functions, electron transport (complexes I-V) and oxidative stress (reactive oxygen species) attenuate mechanical hyperalgesia induced by intradermal injection of psepsilonRACK. In marked contrast, in a PKC epsilon-dependent form of mechanical hyperalgesia induced by prostaglandin E (2), inhibitors of mitochondrial function fail to attenuate hyperalgesia.

In a rat model of vibration-induced acute and chronic musculoskeletal pain, the pro-inflammatory...
### Table 2
**Risk factors in acute perioperative pain for developing chronic pain**

<table>
<thead>
<tr>
<th>Demographics and preoperative state</th>
<th>Female gender</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Younger age</td>
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<td></td>
<td>Pain before surgery</td>
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<td></td>
<td>Preoperative chronic pain</td>
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<tr>
<td>Psychological</td>
<td>Preoperative anxiety</td>
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<td></td>
<td>Preoperative catastrophising</td>
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<td></td>
<td>Preoperative fear</td>
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<td></td>
<td>Preoperative depression</td>
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<tr>
<td>Environmental</td>
<td>Low income</td>
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<td></td>
<td>Low self-rated health</td>
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<tr>
<td></td>
<td>Lack of education</td>
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<tr>
<td>Genetic</td>
<td>Genetic polymorphisms</td>
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<tr>
<td></td>
<td>Pharmacogenomics</td>
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<tr>
<td>Intraoperative</td>
<td>Site (thoracotomy, sternotomy, mastectomy, major limb amputation)</td>
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<tr>
<td></td>
<td>Extent of surgery</td>
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<tr>
<td></td>
<td>Incision type (open versus laparoscopic approach)</td>
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<tr>
<td></td>
<td>Increased duration of surgery</td>
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<tr>
<td></td>
<td>Low (compared to high) volume surgical unit</td>
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<td></td>
<td>Pericostal (versus intracostal) stitches</td>
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<tr>
<td></td>
<td>Intraoperative nerve damage (surgical section, compression, stretching, ischaemia, infection)</td>
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<tr>
<td></td>
<td>Electrocautery</td>
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<tr>
<td>Postoperative</td>
<td>Unrelieved pain</td>
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<td></td>
<td>Severe pain</td>
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<td></td>
<td>High postoperative use of analgesics</td>
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<tr>
<td></td>
<td>Surgery performed in previously injured area</td>
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<tr>
<td></td>
<td>Re-operations</td>
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<td></td>
<td>Radiation therapy and chemotherapy (after breast cancer surgery)</td>
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<tr>
<td>Psychological</td>
<td>Emotional numbing</td>
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<tr>
<td></td>
<td>Pain catastrophising</td>
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<td></td>
<td>Fear of movement</td>
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<td></td>
<td>Depression</td>
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<td></td>
<td>Psychological vulnerability</td>
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<td></td>
<td>Stress</td>
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<td>Environmental</td>
<td>Solicitous responding from significant others</td>
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<td></td>
<td>Social support</td>
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<td></td>
<td>Late return to work</td>
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<tr>
<td>Postoperative red flags</td>
<td>Infection</td>
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<tr>
<td></td>
<td>Bleeding</td>
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<td></td>
<td>Organ rupture</td>
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<td>Compartment syndrome</td>
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Reproduced in part from Shipton EA. Post-surgical neuropathic pain. ANZ J Surgery 2008; 548-555; used with permission.
cytokine TNFalpha and the second messenger PKC epsilon, were identified as targets against which therapies might be directed to prevent or treat this common and very debilitating chronic pain syndrome21.

Opioid tolerance and transition of acute to chronic pain

It is of interest that opioid-induced hyperalgesia is PKC-dependent as well. Shared mechanisms for both opioid tolerance and for the transition from acute to chronic pain have been suggested. Repeated intradermal administration of the potent and highly selective mu-opioid agonist, [d-Ala(2),N-MePhe(4),gly-ol]-enkephalin, to produce tolerance due to its inhibition of prosta glandin E(2) hyperalgesia, simultaneously produced hyperalgesic priming. Conversely, injection of the inflammogen, carrageenan, created to use create priming, produced [d-Ala(2),N-MePhe(4),gly-ol]-enkephalin tolerance. Both effects were prevented by inhibition of PKC epsilon22.

Anatomical sites involved (from brain imaging studies)

The cingulate cortex is one of the most frequently activated regions in human pain research23. The anterior cingulate cortex has been implicated in a number of human chronic pain syndromes. The anterior cingulate cortex is activated during both physical pain and social distress, suggesting possible common neurobiological pathways24. The thalamus is frequently activated as well, and its responses correlated with the nociceptive responses in the cingulate cortex25,26.

The potentiation of anterior cingulate cortex neuronal activity induced by thalamic bursting suggests that short-term synaptic plasticities enable the processing of nociceptive information from the medial thalamus. This temporal response variability is particularly important in pain, because temporal maintenance of the response supports cortical integration and memory formation related to noxious events. Moreover, these modifications of cingulate synapses appear to regulate afferent signals associated with persistent peripheral noxious stimulation that may be important in the transition from acute to chronic pain conditions27.

PERIOPERATIVE RISK FACTORS

The transition of acute postoperative pain to chronic post surgical pain is a complex and poorly understood developmental process. Surgical, psychosocial, socio-environmental and patient-related factors28,29 and the known polymorphisms in human genes are involved in perpetuating the pain.

Preoperative risk factors

Preoperative risk factors include being of the female gender, younger age, pain before surgery, preoperative chronic pain, preoperative anxiety, fear and depression and low income, as well as low self-rated health and lack of education (Table 2).

Patients with preoperative pain related (e.g. in the anatomical region of the surgery) or not related (e.g. chronic low back pain) to the surgical site are at significantly greater risk of developing chronic post surgical pain30. This implicates different mechanisms underlying the development of chronic post surgical pain31. The presence or intensity and duration of preoperative pain remains the major risk factor for the development of severe early acute postoperative pain32, as well as for the development of long-term post surgical pain33,34.

Studies have reported that female gender and younger age35 predict intense acute postoperative pain; nationwide surveys consistently find the incidence of chronic neuropathic pain to be significantly higher in women than men26,31,36-38. Several smaller studies of chronic post surgical pain have also identified younger age as a risk factor for the transition from acute pain to chronic post surgical pain29,30,40.

Previous studies have demonstrated that high preoperative anxiety is associated with increased acute postoperative pain24,41, postoperative analgesic consumption24,41 and the development of chronic post surgical pain42,43,44. The impact of preoperative anxiety as a risk factor for chronic post surgical pain has been demonstrated in surgical procedures such as abdominal surgery, breast-cancer surgery and knee replacement surgery46,47.

Greater preoperative catastrophising48,44, and fear of surgery47 have also been associated with the development of chronic post surgical pain. For example, a positive correlation has been found between preoperative scores in catastrophising patients undergoing limb amputation and chronic pain two years postoperatively49. Another study suggests that pain-related fear serves as a risk factor for the development and persistence of chronic pain50.

A previous systematic review found that depression, at least in severe cases, represents a risk factor for the development of chronic post surgical pain50. Geiss and colleagues50 reported that chronically stressed patients with changes in physical reactions to stress are at a higher risk for a poor surgical outcome. Specifically, patients with a hyporeactive hypothalamic-pituitary-adrenal axis are at increased risk for a poor outcome after disc surgery50.
Intraoperative risk factors

Intraoperative risk factors that are associated with an increased likelihood of developing chronic post surgical pain include the following: site (especially following operations with a high incidence of nerve damage, such as thoracotomy, sternotomy, mastectomy, major limb amputation, axillary lymphadenectomy and inguinal hernia repair); extent of surgery and incision type (open versus laparoscopic approach); increased duration of surgery; low (compared to high) volume surgical unit; pericostal (versus intracostal) stitches and intraoperative nerve damage. In the rat model, electrocautery was associated with more chronic pain than the use of a laser (Table 2).

The greatest persistent surgical pain, however, occurs with intentional or unintentional nerve damage. This includes damage to nerves by surgical section, compression (i.e. in a suture or a clip), stretching, ischaemia or infection.

Post-thoracotomy pain syndrome can develop in up to 40% of cases; post-herniorrhaptham pain syndrome in up to 10%; post-amputation pain in up to 50%; and post-mastectomy pain in up to 30% of cases. Poor surgical technique, preoperative pain and poorly controlled postoperative pain have been shown to be associated with the development of persistent post surgical pain. All the above surgeries have in common a high likelihood of nerve damage during the surgery.

Postoperative risk factors

Postoperative risk factors include unrelieved pain, severe pain, high postoperative use of analgesics (over seven days after surgery), surgery performed in a previously injured area and re-operations. Several trials have demonstrated that the intensity of acute postoperative pain predicts the transition to chronic post surgical pain. After breast cancer surgery, radiation therapy and chemotherapy are known risk factors as well (Table 2).

PSYCHOSOCIAL FACTORS

Data on psychological factors and persistent postoperative pain are sparse. The evidence for most factors is weak and heterogeneous. Pain may serve as a traumatic stressor that causes increased emotional numbing. Increased chronic post surgical pain and disability are associated with high concurrent emotional numbing scores at six and 12 months, high levels of pain catastrophising and fear of movement. Cross-sectional studies support a positive relationship between history of traumatic or stressful life events and chronic pain. Social and environmental factors such as solicitous responding from significant others and social support can add to this. A recent systematic review showed that depression, psychological vulnerability, stress and late return to work provided a likely correlation with chronic post surgical pain. Whether psychological and socio-environmental risk factors are associative or causal remains unknown.

GENETIC FACTORS

Genetic factors appear to account for a significant degree of inter-individual variation in pain sensitivity and treatment response. Phenotype variances in pain perception and its modulation are significantly dependent on their genomic determinants. Awareness of individual pain sensitivity and the tendency to develop chronic pain after injury or surgery would be informative for clinical decision-making. The evidence base for pharmacogenomics in acute pain remains small. There have been some consistent outcome studies, but the total number of patients studied is low.

Altered pain sensitivity in the average population has been associated with frequent variants in the micro-opioid receptor gene, catechol-O-methyltransferease gene, guanosine triphosphate cyclohydrolase 1/dopa-responsive dystonia gene, transient receptor potential cation channel, subfamily V, member 1 gene and the melanocortin-1 receptor gene. For example, three common haplotypes of the human catechol-O-methyltransferase gene are associated with experimental pain sensitivity and the onset of temporomandibular joint disorder.

Of interest, one group that would not suffer from chronic post surgical pain are those with ‘channelopathy-associated insensitivities to pain’. However, there are five maladies belonging to the hereditary sensory and autonomic neuropathy I-V syndromes, caused by various mutations in several genes.

Genetic variations can occur during drug uptake, transport, at the effector site, and during the metabolism and excretion of a drug. The ability to identify these genetic polymorphisms may eventually prove to be useful to clinicians in optimising the use of both opioid and non-opioid analgesic medications. With the opioids, pharmacogenomics can influence their response (efficacy, toxicity, pharmacokinetics, metabolism, transport) and contribute to intersubject and interpatient variability. The polymorphic cytochrome P450 enzymes metabolise numerous drugs and show inter-individual variability in their catalytic
activity. Poor metabolisers display a frequency of about 7 to 10% in Caucasian populations. Three to five percent of the Caucasian population are ultrarapid metabolisers, in whom therapeutics effects cannot be obtained with conventional doses. Non-steroidal anti-inflammatory drugs like ibuprofen, naproxen and piroxicam are metabolised by CYP2C9. Between 1 to 3% of Caucasians are poor metabolisers of non-steroidal anti-inflammatory drugs.

PREOPERATIVE EXPERIMENTAL PREDICTORS

Psychophysical measures exploring ‘static’ pain variables (pain thresholds, magnitude estimation of supra-threshold nociceptive stimuli and tolerance) have been regularly reported to predict the intensity of acute postoperative pain in the early phase after surgery. Nevertheless, these measures of response to an acute, phasic, experimental stimulus are less indicative of the complex pain modulation process that occurs after surgery. Some aspects of such modulation can be quantified by using the ‘dynamic’ psychophysical measures of temporal summation and evocation of diffuse noxious inhibitory control, a measure recently reported to predict the risk of chronic post surgical pain after thoracotomy.

A systematic review of 14 studies has investigated the correlation between preoperative responses to experimental pain stimuli and clinical postoperative pain. The experimental stimulation methods used were the cold-pressor test, the heat immersion test, brief phasic or tonic heat stimulation, cutaneous electrical stimulation, pressure algometry, punctate mechanical stimulation and induction of an inflammatory injury.

Preoperative pain tests were found to predict 4 to 54% of the variance in postoperative pain experience depending on the stimulation methods and the test paradigm used. The predictive strength is much higher than previously reported for single factor analyses of demographics and psychological factors. In addition, some of these studies indicate that an increase in preoperative pain sensitivity is associated with a high probability of development of sustained post surgical pain.

PREVENTION OR LIMITATION STRATEGIES

The limitation of nerve and tissue damage during surgery and good multimodal treatment of acute postoperative pain may not only accelerate recovery and rehabilitation and achieve better patient satisfaction after surgery; it may also reduce the risk of persisting chronic pain syndromes (Table 3).

Effective treatment of acute postoperative pain may not only accelerate recovery and rehabilitation and achieve patient satisfaction after surgery, but also reduce the risk of persisting chronic pain syndromes. Chronic pain is difficult to treat. Methods need to be found to prevent or limit the development of persistent post surgical pain. The high incidence of persistent post surgical pain needs to be considered in indications for elective surgery in those who have no pain (e.g., asymptomatic inguinal hernia, vasectomy, breast augmentation) or mild discomfort beforehand. Surgery in patients with backgrounds of hypersensitivity (irritable bowel disease, interstitial cystitis) needs careful consideration as well.

Surgical strategies

Since risk factors related to surgery play a major role, the limitation of nerve and tissue damage during surgery are probably the most important preventative factors. Despite avoidance of traction, stretch, and excessive or prolonged pressure during surgery, perioperative peripheral nerve injuries can and do occur; this is despite appropriate positioning and padding of limbs during surgery.

The least painful surgical approach (e.g., laparoscopic surgery) with acceptable exposure should be used where possible. No large prospective study has confirmed that any specific anaesthetic maintenance technique reduces the risk of chronic post surgical pain.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Prevention and management of risk factors in acute perioperative pain for developing chronic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>Address patient attitudes and concerns Provide education (patient, physician) Identify operative procedures that cause severe pain</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>Use least painful surgical approach (e.g. laparoscopic) with acceptable exposure Use multimodal pharmacological analgesia in addition to afferent neural blockade</td>
</tr>
<tr>
<td>Postoperative</td>
<td>Continue analgesia well into the postoperative period Measure pain levels (the ‘fifth vital sign’) Bedside neurological examination if neuropathic pain is suspected</td>
</tr>
<tr>
<td>Discharge</td>
<td>Individualise discharge analgesic packages and home follow-up Use anticonvulsants (gabapentin and pregabalin) as first-line co-analgesics if needed</td>
</tr>
</tbody>
</table>

Risk factors – mark patients with high risk factors for developing persisting post surgical pain and follow up after discharge.
Pharmacological strategies

Drugs affecting central sensitisation (such as the alpha-2-delta ligands gabapentin and pregabalin, and the NMDA-receptor antagonist ketamine) have been found to be beneficial in some settings.

Multiple high-quality trials have demonstrated analgesic and opioid-sparing efficacy with gabapentin following various surgical procedures. Gabapentin provided better postoperative analgesia and rescue analgesics sparing than placebo in six of 10 randomised controlled trials (RCT) that administered only pre-emptive analgesia. Gabapentin reduces postoperative pain with dose-dependent dizziness and sedation. Gabapentin (and pregabalin) reduce movement-evoked pain, and this can lead to enhanced functional postoperative recovery. Rising evidence shows that gabapentin prevents chronic post surgical pain syndromes.

Pregabalin is a relatively safe and effective medication that may decrease perioperative opioid use in patients with more acute neuropathic pain than acute inflammatory pain. A recent RCT showed that two weeks of perioperative treatment reduced neuropathic pain three and six months after total knee joint replacement from an incidence of 9 and 5%, respectively, to zero. Perioperative pregabalin was found to improve pain and functional outcomes three months after lumbar discectomy. When surgery involves more neuropathic-type acute pain there is growing evidence that pregabalin may decrease the incidence of chronic pain.

Gabapentin and the N-methyl-d-aspartate antagonist, ketamine, are similar in improving early pain control and in decreasing opioid consumption. Ketamine may prevent opioid-induced hyperalgesia as well. The optimal dose of ketamine is still unknown even among similar clinical conditions. One key issue is its safety and tolerability, with psychotomimetic adverse effects being the major concern. However, perioperative low-dose ketamine is both efficacious and preventive as an adjuvant analgesic, with good safety and tolerability profiles. In a Cochrane systematic review, which included 2240 patients, 27 of 37 trials found sub-anaesthetic-dose ketamine to reduce postoperative pain intensity or rescue analgesic consumption, or both. The analgesic efficacy of perioperative ketamine has been demonstrated in most but not all trials conducted after the Cochrane systematic review. In a double-blind RCT with 154 patients undergoing total hip arthroplasty, ketamine reduced both opioid consumption and proportion of patients left with persistent rest pain at day 180 (21% in placebo versus 8% in ketamine group giving an odds ratio of 0.33; 95% confidence interval of 0.12 to 0.91).

Alpha-2 agonists, especially clonidine, seem to be promising with regard to acute postoperative pain management. Clonidine is opioid sparing but is associated with pronounced bradycardia and hypotension in many studies. However, more clinical evidence on the alpha-2 agonist dexmedetomidine is necessary to confirm its role in acute postoperative pain control.

Dexamethasone and methylprednisolone offer analgesia with anti-emesis. Their doses are limited by the steroid-related side effects especially in risk-prone groups such as geriatric patients.

In a recent meta-analysis, systemic lignocaine has been found to improve analgesia, reduce post surgical inflammation and accelerate bowel functional recovery in selected studies focused on abdominal surgery.

In contrast to earlier evidence, magnesium appears to be beneficial especially in abdominal surgery; toxicity is rare when administered as pre-incision loading followed by infusion under vigilant monitoring.

Multimodal analgesic strategies

Standardised pain evaluation and treatment protocols, and the use of multimodal analgesic techniques, should improve perioperative pain management. The benefit-risk ratio for analgesic drug combinations is, therefore, largely dependent on the type of surgery. Highly effective multimodal treatment administered for as long as the surgical stimulus (inflammatory response) continues after the operation will reduce the incidence and severity of chronic post surgical pain.

Central neuraxial techniques and peripheral nerve blocks have become commonplace analgesic adjuncts to major surgical procedures worldwide. Well-constructed randomised controlled trials have demonstrated superior acute perioperative pain relief, reduced systemic complications and improved functional capacity with their use.

Early improved outcomes are achieved by reducing opioid-related side effects. To do this, clinicians need to use rational multimodal analgesic drug combinations (e.g. non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors, paracetamol, gabapentanoids, clonidine, ketamine, and local and regional anaesthetic techniques) that are supplemented by opioid analgesics on an as needed basis. This will lead to more rapid resumption of normal activities of daily living (e.g. mobilisation, recovery of bowel function). The length of hospital stay, the medical and surgical morbidity and the period of post discharge convalescence should be reduced as well.
Only a limited number of well-conducted, prospective randomised clinical trials have demonstrated improved clinical outcomes with respect to analgesia and opioid-related side-effects with multimodal (versus single) therapy\textsuperscript{13}. However, a meta-analysis of single-modality, non-opioid analgesics has demonstrated clinically significant reductions (20 to 40\%) in postoperative nausea and vomiting and in sedation\textsuperscript{14}.

In surgery with high risks of neuropathic pain, the preventative use of gabapentin and pregabalin may be considered. The practicing clinician needs to be aware of the available procedure-specific evidence for optimising multimodal perioperative pain management. An optimal procedure-specific analgesic regimen (see Prospect website: www.postoppain.org) should be integrated into an enhanced recovery care program. An enhanced recovery care program allows for early oral feeding, mobilisation and adjustments in other principles of surgical care (e.g. drains, catheters, tubes and monitoring) consistent with the existing evidence in the peer-reviewed literature\textsuperscript{11,12}. Simple and more rational approaches to pain relief directed toward the periphery (that is the surgical wound and surrounding tissues) may offer the greatest promise for advancing acute postoperative pain management\textsuperscript{15}. In the future, local application of long-acting local analgesic formulations, such as depo-bupivacaine, extended-release bupivacaine and topical capsaicin\textsuperscript{13,14}, may eventually obviate the need for catheter delivery systems. Other factors have been identified as contributing to poor postoperative pain management; these include insufficient education and training of doctors and nursing staff and poor communication at various levels\textsuperscript{17}.

**Preventive analgesic strategies**

Studies that compared the same dose of an analgesic given before versus after the surgical stimuli have failed to document any advantages of the so-called pre-emptive approach\textsuperscript{72,18} and the term should probably be dropped. Until recently, studies of preventive multimodal analgesia were equivocal as well\textsuperscript{4}. However, the simple provision of good analgesia in the postoperative period has a preventive effect\textsuperscript{19}. Preventive analgesia is therefore the persistence of analgesic treatment efficacy beyond its expected duration. It holds the most hope for minimising chronic pain after surgery or trauma as it decreases central sensitisation and ‘windup’. Ideally, active intervention should be continued for as long as the sensitising stimulus persists\textsuperscript{19}. Benefits have been found with the use of epidural analgesia after thoracotomy\textsuperscript{20}, colectomy\textsuperscript{20} and amputation\textsuperscript{21}, as well as with the use of paravertebral blockade after mastectomy\textsuperscript{22}. Benefits have even been found with local infiltration or topical administration of local anaesthetics\textsuperscript{23}.

An impressive RCT has recently taken place in patients after hip or knee replacements\textsuperscript{24}. They received either standard-of-care analgesia or good background analgesia with access to breakthrough pain medication, and pre-emptive administration of breakthrough medication one hour before physiotherapy\textsuperscript{25}. When this treatment was given in the first few weeks after surgery, at any follow-up for the next 24 weeks, significantly fewer patients in the group receiving the treatment analgesic regimen had moderate to severe pain on ambulation compared to patients in the control group\textsuperscript{25}. A recent RCT suggested that optimised perioperative analgesia, using epidural analgesia and/or intravenous patient-controlled analgesia, starting 48 hours before and continuing for 48 hours after lower limb amputation to be associated with reduced phantom limb pain intensity, prevalence and frequency six months after amputation\textsuperscript{25}.

It seems important to achieve effective analgesia in the early postoperative period and then ensure that an effective ‘preventive’ analgesic regimen is continued into the post discharge period (for as long as the nociceptive input from the wound persists after surgery)\textsuperscript{72,126-128}.

**Psychological strategies**

Screening questionnaires including psychosocial predictors have already been developed by Hazard and colleagues\textsuperscript{72}, as well as by Linton and Halden\textsuperscript{128}, to assess pain and should be used. Fear beliefs should be assessed and addressed through reassurance that pain does not necessarily equal harm\textsuperscript{25}. For high fear patients, cognitive behavioural therapy may be needed\textsuperscript{26}. Activities should be gradually increased and self-monitoring encouraged. In future, perioperative psychological pain management programs should be developed to help prevent and treat post surgical pain.

**WHAT OF THE FUTURE?**

Pre-existing and current pain, psychological and emotional factors and the social environment all interact with noxious and inflammatory responses to surgical incision and to nerve damage. Damaged nerves, in turn, result in peripheral ectopic activity and central nervous system re-organisation. All these factors can be attenuated by the beneficial effects of preventive multimodal analgesia\textsuperscript{4}.

Increasing knowledge of genetic factors will lead to the designing of more effective pain medications.
with lower adverse effect profiles. Knowledge may increase the ability of clinicians to identify high and low pain responders before surgery, or specific genotypes that may influence the pharmacokinetics of analgesics. Pain genes may yet be identified that confer increased risk of developing intense acute pain and chronic post surgical pain\textsuperscript{3}. Systematic genotype screening could then occur to discriminate populations at risk of developing chronic post surgical pain\textsuperscript{4}. Questionnaires and other tools will need to be constructed to collect clinically relevant phenotypical pain data for genetic studies\textsuperscript{5}. DNA samples using multicentre research teams would need to be collected from individuals with post surgical pain experiences for a comprehensive characterisation of their acute and chronic post surgical pain phenotypes to take place\textsuperscript{6}.

In essence, the nature of central sensitisation during acute and chronic post surgical pain share common features and there may be interactions between acute and persistent postoperative pain\textsuperscript{7}. Chronic pain after surgery is likely to result from a complex combination of mechanisms. The relative contribution of each of these mechanisms to the persistence of pain needs understanding.

Valid preclinical models need to be developed\textsuperscript{8}. To validate animal models against the phenotypes of post surgical pain in humans, testing pain-related behaviour should include withdrawal responses after stimulation and parameters of spontaneous pain\textsuperscript{9}. Patients at higher risk for chronic post surgical pain should be identified. The relationship between prior pain, early postoperative pain and chronic post surgical pain (whether associative or causal) should be fully determined\textsuperscript{10}. Cohorts with previous pain experiences should be explored as well.

Future studies should include a detailed assessment of the location, characteristics and evolution of painful symptoms, associated changes in neurological function, assessment of all of the known risk factors, evidence-based diagnosis of pain and careful description of all procedures\textsuperscript{11}, as well as assessments of the consequences of persistent pain on physical and social function\textsuperscript{12}. A recent meta-analysis showed that failure to distinguish between ‘pain at rest’ and ‘movement-evoked pain’ and to standardise their measurement threatens trial precision and ability to identify interventions with the most clinically relevant effects on pain\textsuperscript{13}. Movement associated pain and measurement of pain at rest should therefore be included in every post surgical trial\textsuperscript{14}.

Future studies should determine which factors in the perioperative pain experience are predictive of the transition to chronic post surgical pain. These include qualities specific to the pain itself (e.g. intensity, quality, duration), or qualities inherent to the individuals reporting the pain (e.g. response bias, psychological vulnerability, genetic predisposition)\textsuperscript{15}. They should be performed on a procedure-specific basis\textsuperscript{16}. A careful study design adhering to these suggestions has recently been published\textsuperscript{17}.

Appropriate therapeutic interventions should then be developed to prevent the development of persistent post surgical pain. Adjuvants should in future be incorporated into a practical regime based on procedure-specific multimodal analgesia\textsuperscript{18}. Their perioperative opioid-sparing benefits should be expanded into the prevention of chronic post surgical pain\textsuperscript{19}. The specific part of the pain pathway affected by an insult should be targeted as well.

With the global increase in healthcare costs, the social costs and the economics of preventive therapies for chronic post surgical pain need to be carefully considered. Unfortunately, there is no data to determine whether patients who have not experienced chronic pain would consider its prevention after surgery important enough to undergo preoperative, intraoperative and postoperative analgesic interventions\textsuperscript{20}.

REFERENCES


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