Pain 1

Treatment of acute postoperative pain

Christopher L Wu, Srinivasa N Raja

Although postoperative pain remains incompletely controlled in some settings, increased understanding of its mechanisms and the development of several therapeutic approaches have substantially improved pain control in past years. Advances in our understanding of the process of nociception have led to insight into gene-based pain therapy, the development of acute opioid-induced hyperalgesia, and persistent postsurgical pain. Use of specific analgesic techniques such as regional analgesia could improve patient outcomes. We also examine the development of new analgesic agents and treatment modalities and regimens for acute postoperative pain.

Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University and School of Medicine, Baltimore, MD, USA (Prof C L Wu MD, Prof S N Raja MD)

Correspondence to:
Prof Christopher L Wu,
Johns Hopkins Hospital,
Baltimore, MD 21287, USA
chwu@jhmi.edu

Introduction

The treatment of acute postoperative pain is an important health-care issue. Many advances have been made in our understanding of the process of nociception and innovations in both analgesic agents and techniques for provision of analgesia since the last *Lancet* review of the topic.[1] Although there have been many developments in acute postoperative pain during the past decade, we provide the latest perspective on several key areas in the treatment of this form of pain.

Treatment of acute postoperative pain: how are we doing?

During the past two decades, the undertreatment of acute pain has been widely recognised as an important issue in health care. Researchers have estimated that only one in four surgical patients in the USA received adequate relief of acute pain.[2] Acknowledgment of the widespread nature of acute postoperative pain led to the development of many medical societal guidelines and more notably of new regulatory standards (eg, Joint Commission on Accreditation of Healthcare Organizations) for the assessment and management of acute pain. One of the main emphases of these new standards has been the routine assessment of pain as the so-called fifth vital sign.[2]

Despite the introduction of new standards, guidelines, and educational efforts, data from around the world suggest that postoperative pain continues to be under-managed. An assessment of 1490 surgical inpatients in the Netherlands revealed that, despite the presence of an acute pain protocol, 41% of patients had moderate-to-severe pain on the day of surgery, with almost 15% of patients noting the presence of moderate-to-severe pain on the fourth postoperative day.[3] A random sample of 250 US adults who had undergone surgical procedures showed that 80% of patients had acute pain post-operatively and, of these patients, 86% had moderate-to-severe pain, with more patients reporting pain after than before hospital discharge.[4] The continued undertreatment of pain is not limited to adult patients. A study of 261 children undergoing routine tonsillectomy and adenoidectomy noted that on the first day at home,

Search strategy and selection criteria

We searched Medline (between 2000, and July, 2010) and Embase (2000–11) using the search terms "acute pain" or "postoperative pain", and limiting the field to "title/abstract". Although we largely focused on reports published within the past 3 years, we did not exclude commonly referenced and highly regarded older publications. The reference lists of articles identified by this search strategy, several book chapters, and the authors' personal reference lists were also included. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers.

Key messages

- Despite the introduction of new standards, guidelines, and educational efforts, data from around the world suggest that postoperative pain continues to be managed inadequately, although the reasons why are not clear.
- Basic science and clinical data suggest that a paradoxical response to opioids might exist such that patients who receive opioids can actually become more sensitive to painful stimuli, thus resulting in hyperalgesia rather than analgesia (opioid-induced hyperalgesia). The implications of this response for routine postoperative pain management are, however, unclear.
- The issue of individualised genotype-based pain therapy is complex and far from being realised for routine clinical practice. Although there is clearly some genetic component to the perception of pain, the overall clinical effects of common polymorphisms in most patients are small, unlike the large genotype effects seen in rare variants.
- The development of a chronic pain state after surgery, termed persistent postsurgical pain, is being increasingly recognised as a not uncommon occurrence. Several risk determinants for persistent pain have been identified, but no one factor seems to have a dominant role.
- Data suggest that use of specific analgesic agents or techniques, particularly regional analgesia (eg, epidural or peripheral nerve analgesia) with a local anaesthetic-based regimen, can affect major postoperative morbidity. Use of regional analgesic techniques is associated with lower pain scores than are seen with systemic opioids.
- Research into multimodal analgesia does not reveal a consistent level of success in part because of the large number of variables (eg, different doses or analgesic agents or techniques, type of surgery) present in available studies; however, some multimodal analgesia trials have shown improved outcomes (eg, improved analgesia) or even possibly a reduced incidence of chronic postsurgical pain.

parents rated 86% of children as having significant overall pain.[5]

Why there has been little progress in the treatment of acute postoperative pain is unclear, but the causes might be multifactorial, including the continued paucity of pain assessment and documentation, heightened awareness and increased number of audits or surveys leading to increased identification of undertreatment of pain, absence of specific written postoperative pain protocols, deficiencies in educational pain management programmes for health-care workers, underuse of effective analgesic techniques (eg, epidural analgesia and peripheral nerve catheters), and poor adherence to available guidelines.[6–8] The inconsistent progress in the overall treatment of acute postoperative pain has occurred despite a possible increase in the overall use of opioids in an attempt to treat acute and chronic pain.[9–12] This increased opioid use could be associated with an increased incidence of opioid-related adverse drug events, including oversedation and respiratory depression,[13,14] although further studies examining the incidence and risk factors associated with opioid-related side-effects and complications are needed to elucidate possible trends. Further study and vigilance are needed because opioid-related adverse drug events have been associated with an increase in overall cost, length of stay, and even decreased survival during in-hospital resuscitation.[15,16]

Pathophysiology of postoperative pain
Mechanisms
Although a comprehensive overview of the nociceptive processing of acute postoperative pain is beyond the scope of this report, there have been several recent developments in the study of the nociception of acute postoperative pain.[17] Neurophysiological and pharmacological studies in recently developed animal models for postoperative pain have advanced our knowledge of the mechanisms of pain resulting from surgical incision and associated tissue injury.[18–21] These studies suggest that incisional pain differs in its mechanism from other inflammatory or neuropathic pain states. Hyperalgesia in the region of the incision is thought to be mediated by sensitisation of $A\delta$-fibre and C-fibre nociceptors and the conversion of mechanically insensitive or silent $A\delta$ nociceptors to mechanically sensitive fibres after incision.[22] Additional studies show an important role of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA)/kainate ionotropic excitatory aminoacid receptors for incision-induced pain, hyperalgesia, and spinal sensitisation.[23] Increased lactate concentrations and low pH occur in skin and muscle wounds after incision and suggest that an ischaemic pain mechanism might contribute to postsurgical pain.[24] Central neuronal sensitisation probably contributes to postoperative pain and hyperalgesia. Neurophysiological studies in animal models have shown an increase in the prevalence and rate of spontaneous activity of spinal dorsal horn neurons after skin and deep muscle incision.[17] However, the precise role of central sensitisation in the development of persistent postoperative pain is uncertain.[25,26]

Predictors of postoperative pain
In an attempt to improve postoperative pain management, studies have focused on identification of predictors of postoperative pain resulting from various surgical procedures. Preoperative pain, anxiety, young age, obesity, surgical fear, catastrophising, and type of surgery (abdominal, orthopaedic, and thoracic surgery, long duration) have been identified as predictors of postoperative pain.[27,28] Type of surgery, age, and psychological distress also predicted postoperative analgesic consumption. The postulate, which needs to be confirmed with future studies, is that early identification of predictive risk factors for postoperative pain will allow development of effective pain management programmes.

Acute opioid-induced hyperalgesia in the perioperative period
Recent basic science and clinical data suggest that a paradoxical response to opioids might exist such that patients who receive opioids could actually become more sensitive to painful stimuli, thus resulting in hyperalgesia rather than analgesia.[29] This event, known as opioid-induced hyperalgesia (OIH), presumably results from the upregulation of pronociceptive pathways within the central and peripheral nervous systems.[30] Although hyperalgesia has traditionally been associated with chronic pain, acute OIH can occur after intraoperative or postoperative administration of high doses of potent opioids, which can lead to increased postoperative pain despite a concurrent increase in postoperative opioid use.[29–32] OIH is distinctly different pharmacologically from analgesic tolerance to opioids (resulting from the desensitisation of antinociceptive pathways), although both will ultimately result in an increase in opioid requirements.[29] Clinically, differentiation between tolerance and OIH might be difficult.

Direct evidence for the acute development of OIH comes from several volunteer studies in which amplification of experimentally induced hyperalgesia was noted after infusion of remifentanil, a short-acting potent opioid.[29] Acute OIH can occur in various settings including low-dose, high-dose, and maintenance-dose regimens of opioids.[29,30] Although the exact mechanisms of OIH are unclear, available data suggest that glutaminergic system interaction and N-methyl-D-aspartate (NMDA) receptor activation might be important in the development of OIH. Modulation of acute OIH has been reported with α_2 agonists, cyclo-oxygenase (COX)-2 inhibitors, and NMDA receptor antagonists, with most studies examining the use of clinically available NMDA receptor antagonists (ie, ketamine, dextromethorphan, and methadone) in attenuating OIH.[29]

Genetics-based pain therapy

With advances in identification of all the genes in human DNA and understanding of the neurobiology of nociception, there has been hope that genetics-based personalised pain therapy would be feasible, in which preoperative determination of a patient's genotype could guide the choice of analgesic agent and dosage postoperatively.[33,44] There are examples of potential genotyping-tailored treatments in other areas of medicine.[35,36] Furthermore, reports of individuals with a complete inability to sense pain and identification of the mutation (α subunit of the voltage-gated sodium channel Nav1.7, SCN9A)[37] have raised hopes of a clinically relevant genotyping-based pain therapy.

Available studies suggest that several gene candidates could be important in the development of an individualised genetics-based pain therapy. The cytochrome P450 2D6 (*CYP2D6*) gene might affect codeine analgesia, because the CYP2D6 enzyme is needed for prodrug activation (ie, codeine is transformed to morphine). CYP2D6 is a polymorphic enzyme, and genotyping can predict reduced enzyme function.[34] Conversely, *CYP2D6* gene amplification can result in accelerated metabolism of tramadol[38] and morphine (ie, ultrarapid metaboliser), which in rare instances can result in significant toxicity.[39] Another gene candidate that could be influential in treatment of acute pain is the human μ-opioid receptor gene (*OPRM1*) 118A→G variant. Although there are more than 100 identified variants in *OPRM1*,[40] the single nucleotide polymorphism 118A→G is present in up to 17% of the white population and 49% of the Asian population, and might be associated with a reduction in μ-opioid receptor expression or signalling.[41] Other possibilities include genes encoding enzymes related to prostaglandin production (*PTGS2* for the COX-2 gene), which might in part account for the interindividual differences in analgesic responses to COX-2 inhibitors, and to production of ABCB1 (P-glycoprotein) encoding a polymorphic transporter, which might have clinical relevance in identification of patients susceptible to respiratory depression induced by opioids.[42,43]

Despite the promise and potential, the reality of individualised genotype-based pain therapy is far from being realised for routine clinical practice. Although there is clearly some genetic component to the perception of pain, the overall clinical effects of common polymorphisms in most patients are small, unlike the large genotype effects seen in rare variants (eg, *SCN9A*).[34] Another obstacle is that not all variants have been identified and the clinical effects of the currently commonly studied genes have generally been negligible such that routine genotyping would not be able to reliably predict an individual's response to a particular analgesic agent.[33,34] For instance, a meta-analysis of studies examining *OPRM1* 118A→G found no effect of the presence of this variant on pain levels.[41] Ultimately, common gene variants, many of which probably have not been identified, might account for only a small clinical effect.[33,34]

Persistent postsurgical pain

The development of a chronic pain state, termed persistent postsurgical pain (PPP), is increasingly being recognised as a not uncommon sequel of surgery. PPP should be diagnosed when pain persists beyond the expected healing period associated with tissue injury and inflammation (2 months or longer after most surgical procedures) and other causes for the pain have been excluded.[44,45] Although incidence can vary depending on the nature of the surgery, many common operations (eg, mastectomy, thoracotomy, hernia repair, coronary artery bypass surgery, amputation) are associated with an incidence of PPP of up to 30–50%.[44,45] Ongoing inflammation or injury to peripheral nerves during the surgery have been postulated as primary causal factors leading to persistent pain. Much research has focused on understanding of the mechanisms of the transition from acute to chronic pain and predictors of chronic pain, in an attempt to prevent development of PPP (figure 1).[46]

Several risk determinants for PPP have been identified, but no one factor seems to play a dominant part. For example, the intensity of perioperative pain has been suggested as a key risk factor; however, less than 20% of
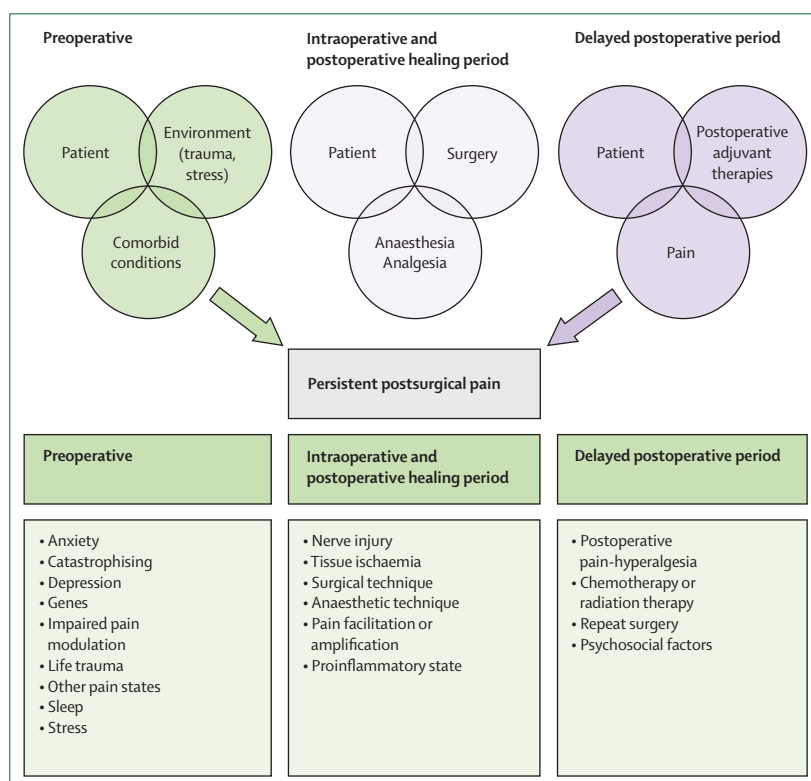
Figure 1: **Potential risk determinants of persistent postsurgical pain**
Multiple inputs (preoperative, intraoperative, and postoperative) can contribute to the development of persistent postsurgical pain.

the overall risk of chronic pain can be predicted by the severity of postoperative pain.[47] Several other surgical, psychosocial, and patient-related genetic and environmental risk factors have been identified.[48] For instance, old age, female sex, obesity, and depression were independent predictors of patient-related pain and function as well as use of pain treatment, 2 and 5 years after revision total hip arthroplasty.[49] Depression, psychological vulnerability, stress, and duration of disability (time to return to work) are the best psychosocial predictors of PPP.

Many analgesic agents and techniques, most notably peripheral nerve blocks and epidural analgesia, can provide preventive analgesia, which is broadly defined as any perioperative regimen used to control pain-induced sensitisation.[25] Preventive measures have focused on aggressive multimodal perioperative analgesic regimens, adjuvant non-opioid therapies such as COX antagonists, α_2-adrenergic agonists, gabapentin, and pregabalin, NMDA antagonists, steroids, and extended regional analgesia with local anaesthetics.[48,49] However, despite some encouraging results, there is no established and definitive evidence for the role of any intervention for the prevention of PPP.

Management of acute pain and patient outcomes

Pathophysiological responses
Acute pain causes a wide range of pathophysiological responses, which are initiated when nociceptors are activated after tissue injury, resulting in a local inflammatory response and subsequent behavioural and physiological responses.[1] After tissue injury, sympathoneural and neuroendocrine activation (along with uncontrolled pain) can ultimately lead to various potentially detrimental responses such as tachycardia, hypertension, hyperglycaemia, immunosuppression, decreased regional blood flow or venous stasis, and platelet aggregation.[1] In high-risk patients (eg, presence of multiple comorbidities, decreased physiological reserves) or those undergoing high-risk procedures, these pathophysiological responses can result in increased morbidity. Some analgesic agents or techniques, such as regional anaesthesia–analgesia with local anaesthetics, used for the treatment of acute postoperative pain can attenuate these pathophysiological responses to a greater extent than that seen with systemic analgesics[50] and result in improvement of some patient outcomes.

Conventional outcomes
Whether the treatment of acute pain might globally affect patient outcomes after surgery is not entirely clear, but data suggest that use of specific analgesic agents or techniques can affect major postoperative morbidity (panel).[51–58] For instance, two large database analyses suggest that postoperative epidural analgesia might be associated with a small but significant reduction in 30-day mortality for patients undergoing major non-cardiac surgery, although this effect should be interpreted cautiously and the absolute magnitude was also small (corresponding to a number needed to treat of 477 in one study).[59,60] For other major morbidities, the data are slightly more compelling. Results of several meta-analyses suggest that use of epidural analgesia or continuous paravertebral blockade is associated with decreased risk of postoperative pulmonary complications in patients undergoing upper abdominal and thoracic surgical procedures.[58,61] The perioperative use of epidural analgesia is also associated with a reduction in respiratory complications after major abdominal surgery, although the effect of epidural analgesia might not be as prominent as it was previously, partly because the incidence of respiratory complication has progressively decreased during past years.[51] Meta-analyses in patients undergoing high-risk cardiothoracic and vascular procedures suggest that use of perioperative thoracic epidural analgesia might decrease pulmonary complications, cardiac dysrhythmias, and overall cardiac complications.[52,53] Finally, perioperative use of either thoracic epidural analgesia or intravenous local anaesthetics are associated with faster resolution of postoperative ileus after major abdominal surgery.[54,61,62] Specific evidence-based recommendations, based on systematic reviews, for postoperative pain management have been made for different surgical procedures.[63]

Patient-centred outcomes
Data suggest that use of one analgesic regimen might have a different effect when compared with another with respect to patient-centred outcomes (eg, analgesia, satisfaction). For instance, use of intravenous patient-controlled analgesia with opioids versus conventional opioid analgesia (eg, a nurse administering an analgesic

---

Panel: Potential benefits of regional anaesthesia–analgesia on patient outcomes

Epidural analgesia[51–56]
- Analgesia: lower pain scores with epidural analgesia than with systemic opioids
- Cardiovascular: reduced risk of myocardial infarction and dysrhythmias (thoracic epidural analgesia in high-risk patients)
- Gastrointestinal: earlier return of bowel function (thoracic epidural analgesia in abdominal surgical procedures)
- Pulmonary: reduced risk of postoperative pulmonary complications (thoracic epidural analgesia in high-risk patients)

Peripheral nerve analgesia[57]
- Analgesia: lower pain scores with peripheral nerve analgesia than with systemic opioids
- Rehabilitation: facilitates earlier rehabilitation goals and reduced length of stay (most studies done in orthopaedic patients)

Paravertebral analgesia[58]
- Analgesia: lower pain scores with paravertebral analgesia compared with systemic opioids
- Pulmonary: reduced risk of postoperative pneumonia in patients undergoing thoracotomy

	Common routes of administration	Probable mechanisms of analgesic action	Potential relevant side-effects
Local anaesthetics (bupivacaine, lidocaine)	EA/SA, PNB/C, SC, TR	Inhibition of sodium channel	Hypotension, motor block, myotoxicity, systemic toxicity (seizures, cardiac dysrhythmias, cardiac arrest) in high doses
Opioids (fentanyl, morphine)	EA/SA, IV, SC, TR	μ-receptor agonist	Sedation, nausea, vomiting, pruritus, respiratory depression, immunosuppression
Paracetamol	PO, IV	Uncertain	Hepatic toxicity and liver failure at high doses, hypersensitivity
Non-steroidal anti-inflammatory agents (celecoxib, ibuprofen, ketorolac)	PO, IV	Inhibition of cyclo-oxygenase	Gastrointestinal irritation, platelet inhibition, renal insufficiency or failure, cardiovascular, hypersensitivity
Gabapentinoids (gabapentin, pregabalin)	PO	Inhibition of voltage-gated sodium channels	Sedation, peripheral oedema, gastrointestinal; decrease dose for renal insufficiency
α_2 agonists (clonidine, dexmedetomidine)	PO, IV	α_2-receptor agonist	Sedation, hypotension, bradycardia

EA/SA=epidural/spinal. PNB/C=peripheral nerve block/catheter. SC=subcutaneous. TR=transdermal. IV=intravenous. PO=oral.

Table: Analgesic agents commonly used for the treatment of acute pain

agent at the patient's request) for postoperative pain control results in improved pain control and increased patient satisfaction.[64] Use of regional analgesic techniques (eg, epidural or peripheral nerve analgesia) with a local anaesthetic-based regimen is associated with significantly lower pain scores than is seen with systemic opioids.[55,57] Despite data suggesting that improved postoperative analgesia leads to improved conventional patient outcomes,[61] there is insufficient evidence to support subsequent improvements in some other patient-centred outcomes such as quality of life and quality of recovery.[56]

Multimodal analgesia and adjuvant agents

The use of multimodal analgesia, a strategy that concurrently uses more than one class of analgesic agent or technique (table), has been advocated as a means to improve analgesia through either additive or synergistic effects while reducing opioid-related side-effects.[65] Although there are many permutations by which analgesics can be combined, multimodal analgesia realistically can be defined as a combination of an opioid and non-opioid analgesic, with or without a regional anaesthetic block, typically resulting in improved analgesia with concurrent reduction in the incidence of some opioid-related side-effects (eg, a decrease in postoperative nausea, vomiting, and sedation), presumably through an opioid-sparing effect.[66,67] As a whole, research into multimodal analgesia does not reveal a consistent level of success, in part because of the large number of variables (eg, different doses or analgesic agents or techniques, type of surgery) present in available studies; however, some multimodal analgesia trials have shown improved outcomes or lowered incidence of chronic postsurgical pain.[68,69] Despite the recent high-profile case of academic fraud that resulted in the retraction of several multimodal analgesia studies, carefully performed systematic reviews seem to be robust against the effect of these reports.[70] In general, the benefits of the combination of non-opioid agents (apart from the combination of paracetamol with non-steroidal anti-inflammatory agents[71]) for multimodal analgesia in the postoperative period are unclear because high-quality, large-scale randomised controlled trials are scarce. Although many adjuvant agents have been used, we describe some of the more promising and novel agents.

Originally designed for the treatment of seizures, gabapentin and pregabalin have been used to treat neuropathic pain and, more recently, postoperative pain. Gabapentin and pregabalin bind to a subunit of the voltage-gated calcium channel, thus inhibiting calcium influx and preventing the release of excitatory neurotransmitters. Systematic reviews of randomised controlled trials suggest that use of gabapentin will decrease postoperative pain, opioid consumption, and opioid-related adverse effects, but might be associated with an increased incidence of sedation.[72,73] Few studies are available on pregabalin for the treatment of acute or postoperative pain. Although a recent systematic review suggested that evidence to support the use of pregabalin in acute pain scenarios might be lacking,[74] studies published subsequent to this review suggested otherwise.[75,76] Additional studies will be needed to elucidate the appropriate dosing regimen, analgesic efficacy (pregabalin), and any long-term benefits of the gabapentinoids on acute postoperative pain.

Dexmedetomidine is an intravenous α_2 agonist that had been used mainly as a sedative and analgesic agent in the intensive care unit setting and might be associated with reduced opioid consumption and improved analgesia when used perioperatively.[65] Prescription of buprenorphine, an opioid analgesic that has partial agonist activity at the μ_1 receptor and antagonist activity at the κ receptor, has increased substantially during the past few years, and patients taking buprenorphine can have severe postoperative pain that might not be easily treated with typical doses of opioids.[77,78] Dexmedetomidine can be useful in the treatment of acute postoperative pain in opioid-tolerant patients treated with buprenorphine;[79] however, additional studies are needed
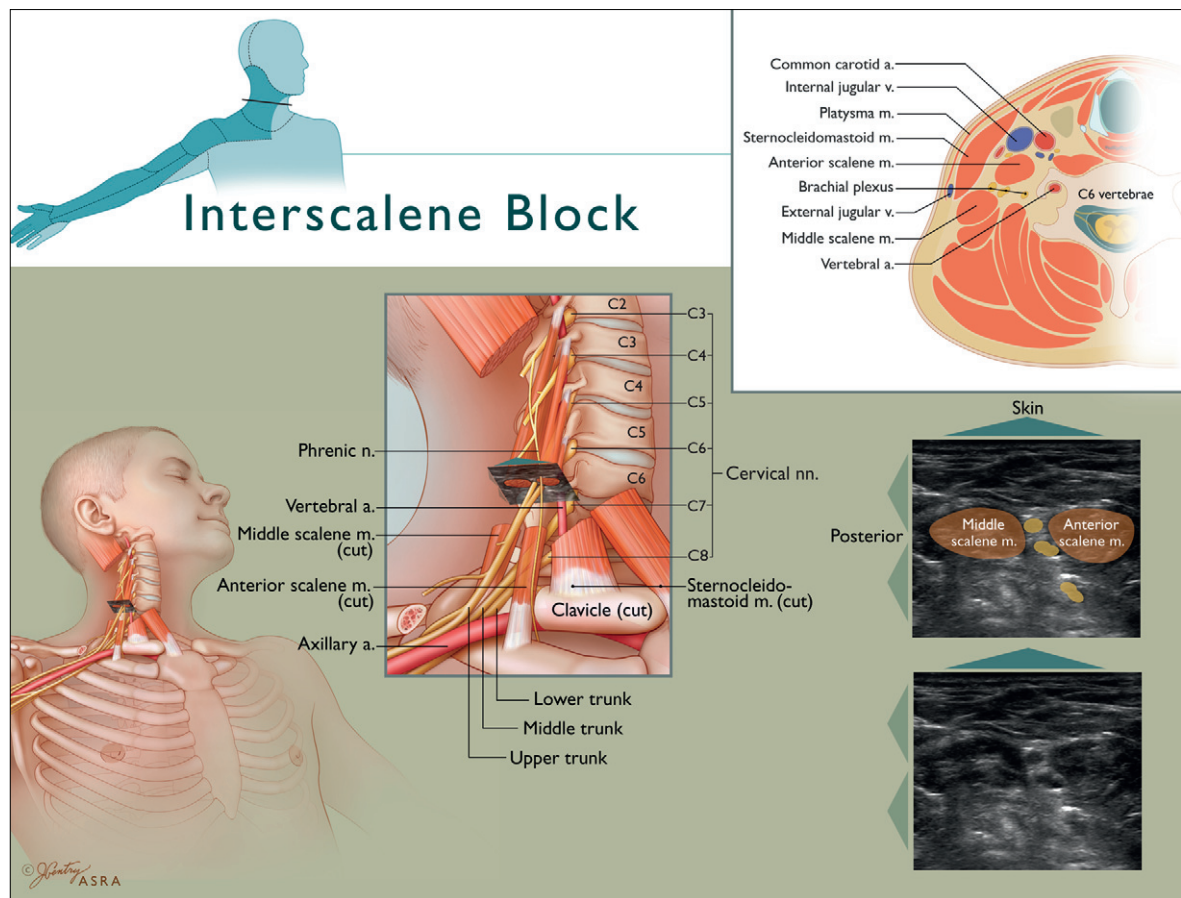
Figure 2: **Anatomy for the interscalene block with ultrasound correlation**
Use of ultrasound can complement our understanding of patient anatomy and thus aid performance of nerve blocks. The upper left inset depicts the expected distribution of anaesthesia after an interscalene nerve block, which can be performed for shoulder surgery. The upper right and lower left insets depict the anatomy relevant for the interscalene nerve block—note the closeness of the brachial plexus to major arteries and the spinal canal. The classic ultrasound view (lower right) depicts the hypoechoic upper roots stacked on each other, within the interscalene groove. Reproduced from reference 74, by permission of the American Society of Regional Anesthesia and Pain Medicine and Jennifer Gentry.

to further define the role of this intravenous agent in multimodal analgesic regimens.

Ketamine is an older anaesthetic agent that can attenuate hyperalgesia related to opioid administration and has seen a resurgence of interest in its new role as an adjunct for multimodal analgesia. One of the reasons for the renewed interest in ketamine is its ability to block the NMDA receptor, which is central in the development of hyperalgesia and tolerance. A recent systematic review of randomised controlled trials of ketamine added to intravenous patient-controlled analgesia with opioids revealed that the addition of a low-dose infusion of ketamine was associated with a significant reduction in pain scores and overall morphine consumption.[80] Although low-dose ketamine infusion does not seem to be associated with an increased incidence of psychomimetic or adverse pharmacological effects,[65] further studies are needed to establish whether there is any long-term benefit in reduction of the incidence or severity of PPP.

Peripheral nerve catheters are another technique that has increased in popularity during the past decade. Anaesthetists can insert these catheters in several locations and, when a local anaesthetic-based analgesic regimen is used, peripheral nerve catheters provide superior analgesia compared with systemic opioids[57] and can result in early mobilisation and possibly reduced length of stay in some instances.[81,82] Some centres will allow use of peripheral catheters on an outpatient basis, further facilitating early discharge and patient recovery. Traditionally, the performance of nerve blocks or catheters for acute postoperative pain control has been with so-called blind techniques such as nerve stimulation of surface anatomy. Increasing use of ultrasound for placement of nerve blocks and catheters allows for real-time visualisation of patient anatomy (figure 2),[83] thus facilitating performance of nerve blocks (figure 3),[84] which can have many benefits including an increased block success rate, decreased time to onset of blocks, and possibly improved quality

of sensory block.[85–87] One of the theoretical benefits of injection of local anaesthetic under ultrasound guidance is a reduction in complication rates such as neurological injuries; however, this possibility has not been definitively proven.[88,89]

## New analgesic agents or techniques

Advances

Although there have been many advances in the development of both analgesic agents and techniques since the previous review,[1] we have only described those that have been used or are very close to being available in the clinical setting. The analgesic agents and techniques described in this section are at different stages of development and might or might not be approved for use, depending on the location of the practitioner.

Sustained-release or extended-release formulations of conventional agents

Although agents such as opioids or local anaesthetics can provide effective pain control when administered as part of epidural or peripheral nerve-block analgesia, the duration of analgesia can be restricted when these agents are administered as a single dose. These agents can be delivered as a continuous infusion via catheters if an extended duration of pain control is desired; however, insertion of these catheters generally requires technical expertise and might be contraindicated in some instances. New formulations of these conventional analgesic agents have been developed to prolong the duration of analgesia to longer than 24 h, and might obviate the need for continuous catheters in some clinical settings.

Extended-release local anaesthetics

Many animal studies have described the administration of extended-release local anaesthetics. Typically, the local anaesthetics have been encapsulated in various biodegradable agents, which when degraded will allow the gradual release of anaesthetics. Local anaesthetics have been reported to be encapsulated in liposomes, liposphères, polyglycolic acid microspheres, and hydrogels.[90] Many animal studies have shown an extended duration of analgesia with these agents.[90,91] Some clinical data also suggest that extended-release local anaesthetics might significantly prolong the duration of action of commonly used local anesthetics;[90,92] however, there are concerns about adverse effects such as neurotoxicity and myotoxicity.[93] Although the available data suggest that the duration of local anaesthetic can be prolonged by a period of several days, few clinical studies have been done and further safety studies will be needed before extended-release local anaesthetics can be routinely used in the clinical setting. Despite extensive research, none of the formulations are currently available for clinical use.
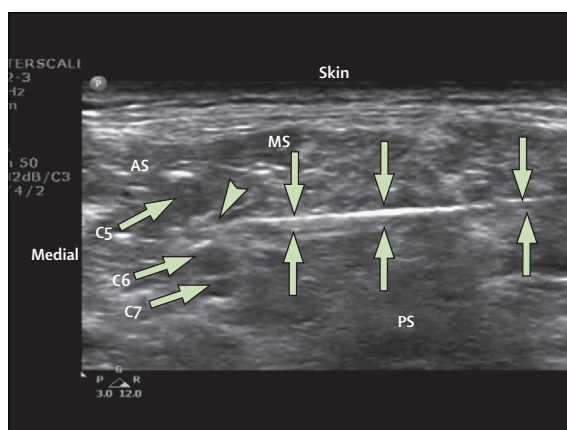
***Figure 3:* Insertion of a needle into the sheath of the brachial plexus under ultrasound guidance**
The bevel of the needle (arrowhead) is seen as it enters the sheath of the brachial plexus (between the C5 and C6 nerve roots). The triangle shows the tip of the needle facing towards the skin and the large arrows outline the needle shaft. Reproduced from reference 75, by permission of Wolters Kluwer Health. AS=anterior scalene muscle. C=cervical. MS=middle scalene muscle. PS=posterior scalene muscle.

Extended-release epidural morphine

Morphine is commonly administered as one dose into the epidural or intrathecal space for postoperative analgesia, and the typical duration of analgesia is 12–24 h after administration. Continuous epidural analgesia with a local anaesthetic-based regimen might be preferred if analgesia is needed for longer than 24 h; however, this modality is contraindicated in some instances such as concurrent anticoagulation with specific agents or regimens.[94] An extended-release formulation of epidural morphine, which is enclosed in microscopic lipid-based particles, is available clinically and has been shown to provide postoperative pain relief for 48 h after a single dose.[95] Despite the extended duration of analgesia without the need for a continuous epidural catheter, a systematic review of available randomised controlled trials of extended-release morphine suggests that this formulation might be associated with an increased incidence of respiratory depression when compared with intravenous patient-controlled analgesia with morphine.[96]

Iontophoretic transdermal delivery of fentanyl

The traditional (passive) transdermal formulation of fentanyl is not recommended for routine treatment of acute or postoperative pain in opioid-naive patients, in part because it can take about 6–12 h to obtain analgesic plasma fentanyl concentrations after application of the transdermal fentanyl patch. A newer formulation of this fentanyl transdermal system has been developed and uses a low-intensity direct current (iontophoresis) to allow for a more rapid transfer of fentanyl from the patch into the skin and local circulation.[97] This type of fentanyl patch allows the patient to activate a demand dose of 40 µg of fentanyl with a lockout interval of 10 min—in

essence, transdermal patient-controlled analgesia.[98] The available randomised controlled trials suggest that this system provides similar analgesia to that seen with intravenous patient-controlled anaesthesia with morphine.[98,99] The iontophoretic transdermal delivery of fentanyl was previously approved by the US Food and Drug Administration and European regulatory agencies, but was withdrawn voluntarily because of technical challenges. This product is under continued development, but the specific role in acute postoperative pain for this new type of fentanyl patch is still uncertain.

Peripherally acting μ-opioid receptor antagonists

Postoperative ileus is a complication of surgery that can be associated with increases in patient morbidity, hospital costs, and length of stay in hospital. Although the cause of postoperative ileus is typically multifactorial, opioids used to treat acute pain can exacerbate postoperative ileus. Peripherally acting μ-opioid receptor antagonists (ie, methylnaltrexone and alvimopan) have been developed to attenuate the adverse effects of opioids on postoperative ileus while providing analgesia.[100] The available trials suggest that peripherally acting μ-opioid receptor antagonists seem to accelerate return of gastrointestinal function in patients undergoing bowel resection without compromising centrally mediated opioid analgesia.[101,102] Both methylnaltrexone and alvimopan are available clinically and seem to be well tolerated; however, there is some concern about the use of alvimopan, which was associated with a raised incidence of myocardial infarction in one study.[102] As with other new agents, the precise role of these agents in the treatment of acute pain has yet to be established, but they might be of benefit to patients who have postoperative paralytic ileus.

Continuous infusions of local anaesthetics

Subcutaneous infiltration of local anaesthetics has long been used for postoperative pain management; however, the analgesic efficacy is limited to the duration of analgesia of the local anaesthetic (typically 4–8 h at most). During the past decade, there has been increasing interest in the use of disposable elastomeric devices that allow infusion of local anaesthetics over a period of days and on an outpatient basis. This fairly straightforward technique typically involves the surgeon directly placing catheters into wounds at the end of the surgical procedure, can be widely used, is technically efficient, and provides reasonable analgesia with a reduction in need for opioids and their related side-effects.[103] One concern with the infusion of local anaesthetics intra-articularly is the association of this technique with catastrophic chrondrolysis.[104]

Complementary and alternative modalities

Several complementary and alternative modalities for postoperative analgesia have been investigated to some extent, although the number of high-quality studies is low. Perioperative acupuncture might be a valuable adjunct for acute postoperative pain management, because a systematic review incorporating 15 randomised controlled trials noted a significant decrease in opioid consumption, risk of opioid-related side-effects (eg, nausea), and postoperative pain intensity at 8 and 72 h in the acupuncture group.[105] Another systematic review of randomised clinical trials on the treatment of postoperative pain with auricular acupuncture noted that in eight of nine trials, auricular acupuncture was superior to control for reduction of postoperative pain.[106] Systematic reviews examining transcutaneous electrical stimulation (TENS) for postoperative analgesia suggest that TENS might be associated with decreased use of postoperative analgesic agents and might be useful as an adjunct to other treatments for moderate post-thoracotomy pain.[107,108] The advantages of other modalities are less clear. Listening to music during acute postoperative pain might be associated with a reduction in pain and opioid requirements; however, the overall extent of these benefits is small and their clinical importance is uncertain.[109] The efficacy of relaxation therapy, massage, or hypnosis or intraoperative suggestion on treatment of acute postoperative pain is uncertain at this time, because of the paucity of high-quality data.[110,111]

Conclusion

Although postoperative pain remains incompletely controlled in some settings and the reasons why are not entirely clear, a comprehensive understanding of its mechanisms and the development of several therapeutic approaches have substantially improved pain control in past years. The use of more effective analgesic techniques (eg, regional analgesia) might be helpful not only for provision of superior analgesia, but also for improvement of conventional outcomes, particularly in high-risk patients or those undergoing high-risk surgical procedures. Finally, additional studies on predictors of postoperative pain and persistent postsurgical pain, efficacy of specific multimodal analgesic regimens, and growth of promising new technologies might lead to substantial gains in the treatment of acute postoperative pain and potential reduction in the development of persistent pain states.

References

1   Carr DB, Goudas LC. Acute pain. *Lancet* 1999; **353:** 2051–58.

2   Phillip DM. JCAHO Pain management standards are unveiled. *JAMA* 2000; **284:** 428–29.

3   Sommer M, de Rijke JM, van Kleef M, et al. The prevalence of postoperative pain in a sample of 1490 surgical inpatients. *Eur J Anaesthesiol* 2008; **25:** 267–74.

4   Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg* 2003; **97:** 534–40.

5   Fortier MA, MacLaren JE, Martin SR, Perret-Karimi D, Kain ZN. Pediatric pain after ambulatory surgery: where's the medication? *Pediatrics* 2009; **124:** e588–95.

6   Benhamou D, Berti M, Brodner G, et al. Postoperative Analgesic THerapy Observational Survey (PATHOS): a practice pattern study in 7 central/southern European countries. *Pain* 2008; **136:** 134–41.

7   Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 2003; **290:** 2455–63.

8   Fletcher D, Fermanian C, Mardaye A, Aegerter P; Pain and Regional Anesthesia Committee of the French Anesthesia and Intensive Care Society (SFAR). A patient-based national survey on postoperative pain management in France reveals significant achievements and persistent challenges. *Pain* 2008; **137:** 441–51.

9   Frasco PE, Sprung J, Trentman TL. The impact of the joint commission for accreditation of healthcare organizations pain initiative on perioperative opiate consumption and recovery room length of stay. *Anesth Analg* 2005; **100:** 162–68.

10 Ritsema TS, Kelen GD, Pronovost PJ, Pham JC. The national trend in quality of emergency department pain management for long bone fractures. *Acad Emerg Med* 2007; **14:** 163–69.

11 Zaslansky R, Hertz D, Brill S, Or J, Meissner W, Halpern P. Tracking the effects of policy changes in prescribing analgesics in one emergency department: a 10-year analysis. *Eur J Emerg Med* 2010; **17:** 56–58.

12 Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. *Pain Physician* 2010; **13:** 401–35.

13 Vila H Jr, Smith RA, Augustyniak MJ, et al. The efficacy and safety of pain management before and after implementation of hospital-wide pain management standards: is patient safety compromised by treatment based solely on numerical pain ratings? *Anesth Analg* 2005; **101:** 474–80.

14 White PF, Kehlet H. Improving pain management: are we jumping from the frying pan into the fire? *Anesth Analg* 2007; **105:** 10–12.

15 Oderda GM, Said Q, Evans RS, et al. Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay. *Ann Pharmacother* 2007; **41:** 400–06.

16 Fecho K, Jackson F, Smith F, Overdyk FJ. In-hospital resuscitation: opioids and other factors influencing survival. *Ther Clin Risk Manag* 2009; **5:** 961–68.

17 Brennan TJ. Pathophysiology of postoperative pain. *Pain* 2011; **152 (3 suppl):** S33–40.

18 Brennan TJ, Vandermeulen EP, Gebhart GF. Characterization of a rat model of incisional pain. *Pain* 1996; **64:** 493–501.

19 Buvanendran A, Kroin JS, Kerns JM, Nagalla SN, Tuman KJ. Characterization of a new animal model for evaluation of persistent postthoracotomy pain. *Anesth Analg* 2004; **99:** 1453–60.

20 Martin TJ, Kahn WR, Eisenach JC. Abdominal surgery decreases food-reinforced operant responding in rats: relevance of incisional pain. *Anesthesiology* 2005; **103:** 629–37.

21 Pogatzki-Zahn EM, Zahn PK, Brennan TJ. Postoperative pain—clinical implications of basic research. *Best Pract Res Clin Anaesthesiol* 2007; **21:** 3–13.

22 Pogatzki EM, Gebhart GF, Brennan TJ. Characterization of Adelta- and C-fibers innervating the plantar rat hindpaw one day after an incision. *J Neurophysiol* 2002; **87:** 721–31.

23 Zahn PK, Umali E, Brennan TJ. Intrathecal non-NMDA excitatory amino acid receptor antagonists inhibit pain behaviors in a rat model of postoperative pain. *Pain* 1998; **74:** 213–23.

24 Kim TJ, Freml L, Park SS, Brennan TJ. Lactate concentrations in incisions indicate ischemic-like conditions may contribute to postoperative pain. *J Pain* 2007; **8:** 59–66.

25 Lavand'homme P. From peripheral to preventive analgesia. Time to reconsider the role of perioperative peripheral nerve blocks? *Reg Anesth Pain Med* 2011; **36:** 4–6.

26 Brennan TJ, Kehlet H. Preventive analgesia to release wound hyperalgesia and persistent postsurgical pain: not an easy path. *Anesthesiology* 2005; **103:** 681–83.

27 Sommer M, de Rijke JM, van Kleef M, et al. Predictors of acute postoperative pain after elective surgery. *Clin J Pain* 2010; **26:** 87–94.

28 Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology* 2009; **111:** 657–77.

29 Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin J Pain* 2008; **24:** 479–96.

30 Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2006; **104:** 570–87.

31 Célèrier E, Rivat C, Jun Y, et al. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. *Anesthesiology* 2000; **92:** 465–72.

32 Joly V, Richebe P, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 2005; **103:** 147–55.

33 Mogil JS. Are we getting anywhere in human pain genetics. *Pain* 2009; **146:** 231–32.

34 Lotsch J, Geisslinger G. A critical appraisal of human genotyping for pain therapy. *Trends Pharmacol Sci* 2010; **31:** 312–17.

35 Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009; **360:** 363–75.

36 Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. *Clin Pharmacol Ther* 2008; **83:** 460–70.

37 Cox JJ, Reimann F, Nicholas AK, et al. An SCN9A channelopathy causes congenital inability to experience pain. *Nature* 2006; **444:** 894–98.

38 García-Quetglas E, Azanza JR, Sádaba B, Muñoz MJ, Gil I, Campanero MA. Pharmacokinetics of tramadol enantiomers and their respective phase I metabolites in relation to CYP2D6 phenotype. *Pharmacol Res* 2007; **55:** 122–30.

39 Ciszkowski C, Madadi P. Codeine, ultrarapid-metabolism genotype, and postoperative death. *N Engl J Med* 2009; **361:** 827–28.

40 Somogyi AA, Barratt DT, Coller JK. Pharmacogenetics of opioids. *Clin Pharmacol Ther* 2007; **81:** 429–44.

41 Walter C, Lotsch J. Meta-analysis of the relevance of the OPRM1 118A.G genetic variant for pain treatment. *Pain* 2009; **146:** 270–75.

42 Lee YS, Kim H, Wu TX, Wang XM, Dionne RA. Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. *Clin Pharmacol Ther* 2006; **79:** 407–18.

43 Park HJ, Shinn HK, Ryu SH, Lee HS, Park CS, Kang JH. Genetic polymorphisms in the ABCB1 gene and the effects of fentanyl in Koreans. *Clin Pharmacol Ther* 2007; **81:** 539–46.

44 Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth* 2008; **101:** 77–86.

45 Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; **367:** 1618–25.

46 Hinrichs-Rocker A, Schulz K, Järvinen I, Lefering R, Simanski C, Neugebauer EA. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP)—a systematic review. *Eur J Pain* 2009; **13:** 719–30.

47 Eisenach JC. Treating and preventing chronic pain: a view from the spinal cord—Bonica Lecture, ASRA Annual Meeting, 2005. *Reg Anesth Pain Med* 2006; **31:** 146–51.

48 Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Rev Neurother* 2009; **9:** 723–44.

49 Singh JA, Lewallen D. Age, gender, obesity, and depression are associated with patient-related pain and function outcome after revision total hip arthroplasty. *Clin Rheumatol* 2009; **28:** 1419–30.

50 Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. *Br J Anaesth* 2001; **87:** 62–72.

51 Wijeysundera DN, Beattie WS, Austin PC, Hux JE, Laupacis A. Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. *Lancet* 2008; **372:** 562–69.

52 Wu CL, Hurley RW, Anderson GF, Herbert R, Rowlingson AJ, Fleisher LA. Effect of postoperative epidural analgesia on morbidity and mortality following surgery in medicare patients. *Reg Anesth Pain Med* 2004; **29:** 525–33.

53 Liu SS, Wu CL. Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. *Anesth Analg* 2007; **104:** 689–702.

54 Joshi GP, Bonnet F, Shah R, et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. *Anesth Analg* 2008; **107:** 1026–40.

55 Pöpping DM, Elia N, Marret E, Remy C, Tramèr MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. *Arch Surg* 2008; **143:** 990–99.

56 Liu SS, Block BM, Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. *Anesthesiology* 2004; **101:** 153–61.

57 Nishimori M, Ballantyne JC, Low JH. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. *Cochrane Database Syst Rev* 2006; **3:** CD005059.

58 Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. *Br J Surg* 2008; **95:** 1331–38.

59 Marret E, Remy C, Bonnet F; Postoperative Pain Forum Group. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. *Br J Surg* 2007; **94:** 665–73.

60 Fischer HB, Simanski CJ, Sharp C, et al. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following total knee arthroplasty. *Anaesthesia* 2008; **63:** 1105–23.

61 Hudcova J, McNicol E, Quah C, Lau J, Carr DB. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. *Cochrane Database Syst Rev* 2006; **4:** CD003348.

62 Richman JM, Liu SS, Courpas G, et al. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. *Anesth Analg* 2006; **102:** 248–57.

63 Wu CL, Cohen SR, Richman JM, et al. Efficacy of postoperative patient-controlled and continuous infusion epidural analgesia versus intravenous patient-controlled analgesia with opioids: a meta-analysis. *Anesthesiology* 2005; **103:** 1079–88.

64 Liu SS, Wu CL. The effect of analgesic technique on postoperative patient-reported outcomes including analgesia: a systematic review. *Anesth Analg* 2007; **105:** 789–808.

65 Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol* 2009; **22:** 588–93.

66 Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. *Anesthesiology* 2005; **102:** 1249–60.

67 Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. *Br J Anaesth* 2005; **94:** 505–13.

68 Buvanendran A, Kroin JS, Tuman KJ, et al. Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement: a randomized controlled trial. *JAMA* 2003; **290:** 2411–18.

69 Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg* 2010; **110:** 199–207.

70 Marret E, Elia N, Dahl JB, et al. Susceptibility to fraud in systematic reviews: lessons from the Reuben case. *Anesthesiology* 2009; **111:** 1279–89.

71 Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg* 2010; **110:** 1170–79.

72 Peng PW, Wijeysundera DN, Li CC. Use of gabapentin for perioperative pain control—a meta-analysis. *Pain Res Manag* 2007; **12:** 85–92.

73 Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. *Reg Anesth Pain Med* 2006; **31:** 237–47.

74 Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev* 2009; **3:** CD007076.

75 Peng PW, Li C, Farcas E, et al. Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy. *Br J Anaesth* 2010; **105:** 155–61.

76 Kim SY, Jeong JJ, Chung WY, Kim HJ, Nam KH, Shim YH. Perioperative administration of pregabalin for pain after robot-assisted endoscopic thyroidectomy: a randomized clinical trial. *Surg Endosc* 2010; **24:** 2776–81.

77 Mark TL, Kassed CA, Vandivort-Warren R, Levit KR, Kranzler HR. Alcohol and opioid dependence medications: prescription trends, overall and by physician specialty. *Drug Alcohol Depend* 2009; **99:** 345–49.

78 Marcucci C, Fudin J, Thomas P, Sandson NB, Welsh C. A new pattern of buprenorphine misuse may complicate perioperative pain control. *Anesth Analg* 2009; **108:** 1996–97.

79 Brummett CM, Trivedi KA, Dubovoy AV, Berland DW. Dexmedetomidine as a novel therapeutic for postoperative pain in a patient treated with buprenorphine. *J Opioid Manag* 2009; **5:** 175–79.

80 Carstensen M, Møller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. *Br J Anaesth* 2010; **104:** 401–06.

81 Fredrickson MJ, Krishnan S, Chen CY. Postoperative analgesia for shoulder surgery: a critical appraisal and review of current techniques. *Anaesthesia* 2010; **65:** 608–24.

82 Ilfeld BM, Mariano ER, Girard PJ, et al. A multicenter, randomized, triple-masked, placebo-controlled trial of the effect of ambulatory continuous femoral nerve blocks on discharge-readiness following total knee arthroplasty in patients on general orthopaedic wards. *Pain* 2010; **150:** 477–84.

83 Neal JM, Gerancher JC, Hebl JR, et al. Upper extremity regional anesthesia: essentials of our understanding, 2008. *Reg Anesth Pain Med* 2009; **34:** 134–70.

84 Antonakakis JG, Sites BD, Shiffrin J. Ultrasound-guided approach for the placement of a continuous interscalene catheter. *Reg Anesth Pain Med* 2009; **34:** 64–68.

85 Liu SS, Ngeow J, John RS. Evidence basis for ultrasound-guided block characteristics: onset, quality, and duration. *Reg Anesth Pain Med* 2010; **35** (2 suppl): S26–35.

86 Neal JM, Brull R, Chan VW, et al. The ASRA evidence-based medicine assessment of ultrasound-guided regional anesthesia and pain medicine: executive summary. *Reg Anesth Pain Med* 2010; **35** (2 suppl): S1–9.

87 Liu SS, Ngeow JE, Yadeau JT. Ultrasound-guided regional anesthesia and analgesia: a qualitative systematic review. *Reg Anesth Pain Med* 2009; **34:** 47–59.

88 Abrahams MS, Aziz MF, Fu RF, Horn JL. Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block: a systematic review and meta-analysis of randomized controlled trials. *Br J Anaesth* 2009; **102:** 408–17.

89 Neal JM. Ultrasound-guided regional anesthesia and patient safety: an evidence-based analysis. *Reg Anesth Pain Med* 2010; **35** (2 suppl): S59–67.

90 Weiniger CF, Golovanevski M, Sokolsky-Papkov M, Domb AJ. Review of prolonged local anesthetic action. *Expert Opin Drug Deliv* 2010; **7:** 737–52.

91 Wang CF, Djalali AG, Gandhi A, et al. An absorbable local anesthetic matrix provides several days of functional sciatic nerve blockade. *Anesth Analg* 2009; **108:** 1027–33.

92 Grant GJ, Barenholz Y, Bolotin EM, et al. A novel liposomal bupivacaine formulation to produce ultralong-acting analgesia. *Anesthesiology* 2004; **101:** 133–37.

93 Padera R, Bellas E, Tse JY, Hao D, Kohane DS. Local myotoxicity from sustained release of bupivacaine from microparticles. *Anesthesiology* 2008; **108:** 921–28.

94 Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; **35:** 64–101.

95 Viscusi ER, Martin G, Hartrick CT, Singla N, Manvelian G; EREM Study Group. Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. *Anesthesiology* 2005; **102:** 1014–22.

96 Sumida S, Lesley MR, Hanna MN, Murphy JD, Kumar K, Wu CL. Meta-analysis of the effect of extended-release epidural morphine versus intravenous patient-controlled analgesia on respiratory depression. *J Opioid Manag* 2009; **5:** 301–05.

97 Viscusi ER, Reynolds L, Chung F, Atkinson LE, Khanna S. Patient-controlled transdermal fentanyl hydrochloride *vs* intravenous morphine pump for postoperative pain: a randomized controlled trial. *JAMA* 2004; **291:** 1333–41.

98 Viscusi ER, Reynolds L, Tait S, Melson T, Atkinson LE. An iontophoretic fentanyl patient-activated analgesic delivery system for postoperative pain: a double-blind, placebo-controlled trial. *Anesth Analg* 2006; **102:** 188–94.

99 Minkowitz HS, Yarmush J, Donnell MT, Tonner PH, Damaraju CV, Skowronski RJ. Safety and tolerability of fentanyl iontophoretic transdermal system: findings from a pooled data analysis of four clinical trials. *J Opioid Manag* 2010; **6:** 203–10.

100 Becker G, Blum HE. Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. *Lancet* 2009; **373:** 1198–206.

101 Viscusi ER, Gan TJ, Leslie JB, et al. Peripherally acting mu-opioid receptor antagonists and postoperative ileus: mechanisms of action and clinical applicability. *Anesth Analg* 2009; **108:** 1811–22.

102 Yeh YC, Klinger EV, Reddy P. Pharmacologic options to prevent postoperative ileus. *Ann Pharmacother* 2009; **43:** 1474–85.

103 Barrington MJ, Watts SA, Gledhill SR, et al. Preliminary results of the Australasian Regional Anaesthesia Collaboration: a prospective audit of more than 7000 peripheral nerve and plexus blocks for neurologic and other complications. *Reg Anesth Pain Med* 2009; **34:** 534–41.

104 Liu SS, Richman JM, Thirlby RC, Wu CL. Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. *J Am Coll Surg* 2006; **203:** 914–32.

105 Sun Y, Gan TJ, Dubose JW, Habib AS. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. *Br J Anaesth* 2008; **101:** 151–60.

106 Usichenko TI, Lehmann Ch, Ernst E. Auricular acupuncture for postoperative pain control: a systematic review of randomised clinical trials. *Anaesthesia* 2008; **63:** 1343–48.

107 Bjordal JM, Johnson MI, Ljunggreen AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur J Pain* 2003; **7:** 181–88.

108 Freynet A, Falcoz PE. Is transcutaneous electrical nerve stimulation effective in relieving postoperative pain after thoracotomy? *Interact Cardiovasc Thorac Surg* 2010; **10:** 283–88.

109 Cepeda MS, Carr DB, Lau J, Alvarez H. Music for pain relief. *Cochrane Database Syst Rev* 2006; **2:** CD004843.

110 Kwekkeboom KL, Gretarsdottir E. Systematic review of relaxation interventions for pain. *J Nurs Scholarsh* 2006; **38:** 269–77.

111 Accardi MC, Milling LS. The effectiveness of hypnosis for reducing procedure-related pain in children and adolescents: a comprehensive methodological review. *J Behav Med* 2009; **32:** 328–39.