

1. PHYSIOLOGY AND PSYCHOLOGY OF ACUTE PAIN

1.1 APPLIED PHYSIOLOGY OF PAIN

1.1.1 Definition of acute pain

Pain is defined by the International Association for the Study of Pain (IASP) as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’ (Merskey & Bogduk, 1994). However, the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of suitable pain-relieving treatment. This emphasises the need for appropriate assessment and management of pain when caring for unconscious patients, preverbal or developmentally delayed children, and individuals with impaired communication skills due to disease or language barriers, as well as those who do not possess a command of the caregiver’s language (Craig, 2006). Even individuals with native command of language and cultural skills can face difficulty in communicating the complexities of the pain experience (Craig, 2009).

Acute pain is defined as ‘pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease’. Chronic pain ‘commonly persists beyond the time of healing of an injury and frequently there may not be any clearly identifiable cause’ (Ready & Edwards, 1992).

It is increasingly recognised that acute and chronic pain may represent a continuum rather than distinct entities. Increased understanding of the mechanisms of acute pain has led to improvements in clinical management and in the future it may be possible to more directly target the pathophysiological processes associated with specific pain syndromes.

Section 1.1 focuses on the physiology and pathophysiology of the transmission and modulation of painful stimuli (ie nociception). Psychological factors that impact on the experience of pain are outlined in Section 1.2. However, in individual patients, biological, psychological and environmental or social factors will all interact. An integrated biopsychosocial approach to management that also considers patient preferences and prior experiences is encouraged.

1.1.2 Pain perception and nociceptive pathways

The ability of the somatosensory system to detect noxious and potentially tissue-damaging stimuli is an important protective mechanism that involves multiple interacting peripheral and central mechanisms. The neural processes underlying the encoding and processing of noxious stimuli are defined as ‘nociception’ (Loeser & Treede, 2008). In addition to these sensory effects, the perception and subjective experience of ‘pain’ is multifactorial and will be influenced by psychological and environmental factors in every individual.

Peripheral nociceptors

The detection of noxious stimuli requires activation of peripheral sensory organs (nociceptors) and transduction into action potentials for conduction to the central nervous system. Nociceptive afferents are widely distributed throughout the body (skin, muscle, joints, viscera, meninges) and comprise both medium-diameter lightly myelinated A-delta fibres and small-diameter, slow-conducting unmyelinated C-fibres. The most numerous subclass of nociceptor

is the C-fibre polymodal nociceptor, which responds to a broad range of physical (heat, cold, pressure) and chemical stimuli. Thermal sensation is detected by a range of transient receptor potential (TRP) channels (Patapoutian et al, 2009). A number of receptors have been postulated to signal noxious mechanical stimuli, including acid-sensing ion channels (ASICs), TRPs and potassium channels (Woolf & Ma, 2007).

Tissue damage, such as that associated with infection, inflammation or ischaemia, produces disruption of cells, degranulation of mast cells, secretion by inflammatory cells, and induction of enzymes such as cyclo-oxygenase-2 (COX-2). Ranges of chemical mediators act either directly via ligand-gated ion channels or via metabotropic receptors to activate and/or sensitise nociceptors (see Table 1.1). Endogenous modulators of nociception, including proteinases (Russell & McDougall, 2009), pro-inflammatory cytokines (eg TNF α , IL-1 β , IL-6) (Schafers & Sorokin, 2008), anti-inflammatory cytokines (eg IL-10) (Sloane et al, 2009) and chemokines (eg CCL3, CCL2, CX3CL1) (Woolf & Ma, 2007; White & Wilson, 2008), can also act as signalling molecules in pain pathways. Following activation, intracellular kinase cascades result in phosphorylation of channels (such as voltage-gated sodium and TRP channels), alterations in channel kinetics and threshold, and sensitisation of the nociceptor. Neuropeptides (substance P and calcitonin gene-related peptide) released from the peripheral terminals also contribute to the recruitment of serum factors and inflammatory cells at the site of injury (neurogenic oedema). This increase in sensitivity within the area of injury due to peripheral mechanisms is termed peripheral sensitisation, and is manifest as primary hyperalgesia (Woolf & Ma, 2007). Non-steroidal anti-inflammatory drugs (NSAIDs) modulate peripheral pain by reducing prostaglandin E₂ (PGE₂) synthesis by locally induced COX-2. Inflammation also induces changes in protein synthesis in the cell body in the dorsal root ganglion and alters the expression and transport of ion channels and receptors, such as TRPV₁ and opioid receptors respectively, to the periphery (Woolf & Ma, 2007). The latter underlies the peripheral action of opioid agonists in inflamed tissue (Stein et al, 2009).

Table 1.1 Examples of primary afferent and dorsal horn receptors and ligands

Ionotropic receptor	Subtype/subunits	Ligand
TRP	TRPV ₁	heat (>42°C), capsaicin, H ⁺
	TRPV ₂	heat (>53°C)
	TRPV ₃ , TRPV ₄	warm (>32°C)
	TRPM ₈	cool
	TRPA ₁	noxious cold (<17°C)
acid sensing	DRASIC, ASIC	H ⁺
purine	P ₂ X ₃	ATP
serotonin	5HT ₃	5HT
NMDA	NR1, NR2A-D, NR3	glutamate
AMPA	iGluR1/iGluR2 and iGluR3/ iGluR4	glutamate
kainate	iGluR5	glutamate
Metabotropic receptor	Subtype	Ligand
metabotropic glutamate	mGluR _{1,2/3,5}	glutamate
prostanoids	EP1-4	PGE ₂
	IP	PGI ₂

Metabotropic receptor	Subtype	Ligand
histamine	H ₁	HA
serotonin	5HT _{1A'} , 5HT _{4'} , 5HT _{2A}	5HT
bradykinin	B _{1'} , B ₂	BK
cannabinoid	CB ₁ , CB ₂	anandamide
tachykinin	neurokinin-1 (NK ₁)	substance P, neurokinin A
proteinase	PAR ₁₋₄	protease
opioid	mu, delta, kappa	enkephalin, dynorphin, beta-endorphin

Notes: 5HT: serotonin; ASIC: acid sensing ion channel; ATP: adenosine triphosphate; BK: bradykinin; DRASIC: subtype of acid sensing ion channel; iGluR: ionotropic glutamate receptor; mGluP: metabotropic glutamate receptor; NK1: neurokinin-1; P2X3: purinergic receptor subtype; PAR: proteinase-activated receptor; PGE₂: prostaglandin E2; PGI₂: prostacyclin; TRP: transient receptor potential. Others (eg H1, EP1-4, TRPV₂) are designated subtypes of receptors rather than abbreviations.

Sodium channels are important modulators of neuronal excitability, signalling and conduction of neuronal action potentials to the central nervous system (CNS) (Cummins et al, 2007; Momin & Wood, 2008; Dib-Hajj et al, 2009). A rapidly inactivating fast sodium current that is blocked by tetrodotoxin is present in all sensory neurons. This is the principal site of action for local anaesthetics, but as the channel is present in all nerve fibres, conduction in sympathetic and motor neurons may also be blocked. Subtypes of slowly activating and inactivating tetrodotoxin-resistant sodium currents are selectively present on nociceptive fibres. Following injury, changes in sodium channel kinetics contribute to hyperexcitability, and specific alterations in the expression of sodium channels (upregulation or downregulation) occur in different pain states. The importance of sodium channels in pain sensitivity is reflected by the impact of mutations in the SCN9A gene encoding the Na(v)1.7 channel: loss-of-function results in insensitivity to pain whereas gain-of-function mutations produce erythromelalgia and severe pain (Dib-Hajj et al, 2008). However, subtype-selective drugs are not yet available (Momin & Wood, 2008).

The cell bodies of nociceptive afferents that innervate the trunk, limbs and viscera are found in the dorsal root ganglia (DRG), while those innervating the head, oral cavity and neck are in the trigeminal ganglia and project to the brainstem trigeminal nucleus. The central terminals of C and A-delta fibres convey information to nociceptive-specific neurons within laminae I and II of the superficial dorsal horn and also to wide dynamic range neurons in lamina V, which encode both innocuous and noxious information. By contrast, large myelinated A-beta fibres transmit light touch or innocuous mechanical stimuli to deep laminae III and IV.

Pain transmission in the spinal cord

Primary afferent terminals contain excitatory amino acids (eg glutamate, aspartate), peptides (eg substance P, calcitonin gene-related peptide [CGRP]) and neurotrophic factors (eg brain-derived neurotrophic factor [BDNF]), which act as neurotransmitters and are released by different intensity stimuli (Sandkuhler, 2009). Depolarisation of the primary afferent terminal results in glutamate release, which activates postsynaptic ionotropic alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors and rapidly signals information relating to the location and intensity of noxious stimuli. In this 'normal mode' a high intensity stimulus elicits brief localised pain, and the stimulus-response relationship between afferent input and dorsal horn neuron output is predictable and reproducible (Woolf & Salter, 2000).

Summation of repeated C-fibre inputs results in a progressively more depolarised postsynaptic membrane and removal of the magnesium block from the N-methyl-D-aspartate (NMDA) receptor. This is mediated by glutamate acting on ionotropic NMDA receptors and

metabotropic glutamate receptors (mGluR), and by substance P acting on neurokinin-1 (NK₁) receptors. A progressive increase in action potential output from the dorsal horn cell is seen with each stimulus, and this rapid increase in responsiveness during the course of a train of inputs has been termed 'wind-up'. Long-term potentiation (LTP) is induced by higher frequency stimuli, but the enhanced response outlasts the conditioning stimulus, and this mechanism has been implicated in learning and memory in the hippocampus and pain sensitisation in the spinal cord (Sandkuhler, 2009). Behavioural correlates of these electrophysiological phenomena have been seen in human volunteers, as repeated stimuli elicit progressive increases in reported pain (Hansen et al, 2007).

Intense and ongoing stimuli further increase the excitability of dorsal horn neurons. Electrophysiological studies have identified two patterns of increased postsynaptic response: 'windup' is evoked by low frequency C-fibre (but not A-beta fibre) stimuli and is manifest as an enhanced postsynaptic response during a train of stimuli; and 'LTP' is generated by higher frequency stimuli and outlasts the conditioning stimulus. Increases in intracellular calcium due to influx through the NMDA receptor and release from intracellular stores activate a number of intracellular kinase cascades. Subsequent alterations in ion channel and/or receptor activity and trafficking of additional receptors to the membrane increase the efficacy of synaptic transmission. Centrally mediated changes in dorsal horn sensitivity and/or functional connectivity of A-beta mechanosensitive fibres and increased descending facilitation contribute to 'secondary hyperalgesia' (ie sensitivity is increased beyond the area of tissue injury). Windup, LTP and secondary hyperalgesia may share some of the same intracellular mechanisms but are independent phenomena. All may contribute to 'central sensitisation', which encompasses the increased sensitivity to both C and A-beta fibre inputs resulting in hyperalgesia (increased response following noxious inputs) and allodynia (pain in response to low intensity previously non-painful stimuli) (Sandkuhler, 2009).

The intracellular changes associated with sensitisation may also activate a number of transcription factors both in DRG and dorsal horn neurons, with resultant changes in gene and protein expression (Ji et al, 2009). Unique patterns of either upregulation or downregulation of neuropeptides, G-protein coupled receptors, growth factors and their receptors, and many other messenger molecules occur in the spinal cord and DRG in inflammatory, neuropathic and cancer pain. Further elucidation of changes specific to different pain states may allow more accurate targeting of therapy in the future.

In addition to the excitatory processes outlined above, inhibitory modulation also occurs within the dorsal horn and can be mediated by non-nociceptive peripheral inputs, local inhibitory GABAergic and glycinergic interneurons, descending bulbospinal projections, and higher order brain function (eg distraction, cognitive input). These inhibitory mechanisms are activated endogenously to reduce the excitatory responses to persistent C-fibre activity through neurotransmitters such as endorphins, enkephalins, noradrenaline (norepinephrine) and serotonin, and are also targets for many exogenous analgesic agents.

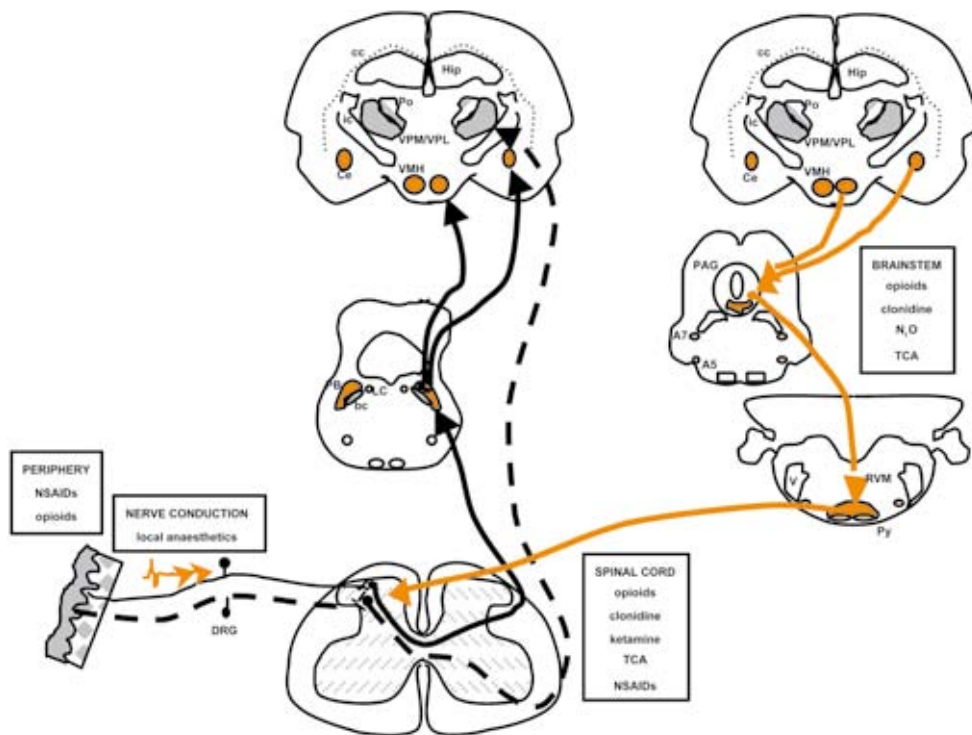
Thus, analgesia may be achieved by either enhancing inhibition (eg opioids, clonidine, antidepressants) or by reducing excitatory transmission (eg local anaesthetics, ketamine).

Central projections of pain pathways

Different qualities of the overall pain experience are subserved by projections of multiple parallel ascending pathways from the spinal cord to the midbrain, forebrain and cortex. The spinothalamic pathway ascends from primary afferent terminals in laminae I and II, via connections in lamina V of the dorsal horn, to the thalamus and then to the somatosensory cortex. This pathway provides information on the sensory-discriminative aspects of pain (ie the site and type of painful stimulus). The spinoreticular (spinoparabrachial) and

spinomesencephalic tracts project to the medulla and brainstem and are important for integrating nociceptive information with arousal, homeostatic and autonomic responses as well as projecting to central areas mediating the emotional or affective component of pain. The spinoparabrachial pathway originates from superficial dorsal horn lamina I neurons that express the NK₁ receptor and projects to the ventromedial hypothalamus and central nucleus of the amygdala. Multiple further connections include those with cortical areas involved in the affective and motivational components of pain (eg anterior cingulate cortex, insular and prefrontal cortex), projections back to the periaqueductal grey (PAG) region of the midbrain and rostroventromedial medulla (RVM), which are crucial for fight or flight responses and stress-induced analgesia, and projections to the reticular formation, which are important for the regulation of descending pathways to the spinal cord (see Figure 1.1) (Hunt & Mantyh, 2001; Tracey & Mantyh, 2007; Tracey, 2008).

Figure 1.1 The main ascending and descending spinal pain pathways



Notes: (a) There are 2 primary ascending nociceptive pathways. The spinoparabrachial pathway (red) originates from the superficial dorsal horn and feeds areas of the brain concerned with affect. The spinothalamic pathway (blue) originates from deeper in the dorsal horn (lamina V) after receiving input from the superficial dorsal horn and predominantly distributes nociceptive information to areas of the cortex concerned with discrimination.

(b) The descending pathway highlighted originates from the amygdala and hypothalamus and terminates in the PAG. Neurons project from here to the lower brainstem and control many of the antinociceptive and autonomic responses that follow noxious stimulation.

Other less prominent pathways are not illustrated.

The site of action of some commonly utilised analgesics are included.

Legend A: adrenergic nucleus; bc: brachium conjunctivum; cc: corpus collosum; Ce: central nucleus of the amygdala; DRG: dorsal root ganglion; Hip: hippocampus; ic: internal capsule; LC: locus coeruleus; PAG: periaqueductal grey; PB: parabrachial area; Po: posterior group of thalamic nuclei; Py: pyramidal tract; RVM: rostroventromedial medulla; V: ventricle; VMH: ventral medial nucleus of the hypothalamus; VPL: ventral posterolateral nucleus of the thalamus; VPM: ventral posteromedial nucleus of the thalamus

Source: Modified from Hunt (Hunt & Mantyh, 2001).

Descending modulatory pain pathways

Descending pathways contribute to the modulation of pain transmission in the spinal cord via presynaptic actions on primary afferent fibres, postsynaptic actions on projection neurons, or via effects on intrinsic interneurons within the dorsal horn. Sources include direct corticofugal and indirect (via modulatory structures such as the PAG) pathways from the cortex, and the hypothalamus, which is important for coordinating autonomic and sensory information. The RVM receives afferent input from brainstem regions (PAG, parabrachial nucleus and nucleus tractus solitarius) as well as direct ascending afferent input from the superficial dorsal horn, and is an important site for integration of descending input to the spinal cord (Millan, 2002). The relative balance between descending inhibition and facilitation varies with the type and intensity of the stimulus and also with time following injury (Vanegas & Schaible, 2004; Heinricher et al, 2009; Tracey & Mantyh, 2007). Serotonergic and noradrenergic pathways in the dorsolateral funiculus (DLF) contribute to descending inhibitory effects (Millan, 2002) and serotonergic pathways have been implicated in facilitatory effects (Suzuki et al, 2004).

1.1.3 Neuropathic pain

Neuropathic pain has been defined as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system' (Merskey & Bogduk, 1994; Loeser & Treede, 2008). Although commonly a cause of chronic symptoms, neuropathic pain can also present acutely following trauma and surgery. The incidence has been conservatively estimated as 3% of acute pain service patients and often it produces persistent symptoms (Hayes et al, 2002). Similarly, acute medical conditions may present with neuropathic pain (Gray, 2008) as discussed further in Section 9.

Nerve injury and associated alterations in afferent input can induce structural and functional changes at multiple points in nociceptive pathways. Damage to peripheral axons results in loss of target-derived growth factors and marked transcriptional changes in DRG of injured neurons (including downregulation of TRP and sodium channels) and a differing pattern in non-injured neighbouring neurons that contributes to spontaneous pain (Woolf & Ma, 2007). In the spinal cord, activation of the same signal transduction pathways as seen following inflammation can result in central sensitisation, with additional effects due to loss of inhibition (Sandkuhler, 2009). Central neurons in the RVM were sensitised after peripheral nerve injury (Carlson et al, 2007) and structural reorganisation in the cortex after spinal cord injury (Wrigley et al, 2009), and changes in cerebral activation have been noted in imaging studies of patients with neuropathic pain (Tracey & Mantyh, 2007).

1.2 PSYCHOLOGICAL ASPECTS OF ACUTE PAIN

Pain is an individual, multifactorial experience influenced, among other things, by culture, previous pain experience, belief, mood and ability to cope. Pain may be an indicator of tissue damage but may also be experienced in the absence of an identifiable cause. The degree of disability experienced in relation to the experience of pain varies; similarly there is individual variation in response to methods to alleviate pain (Eccleston, 2001).

The IASP's definition of pain (Merskey & Bogduk, 1994) emphasises that pain is not a directly observable or measurable phenomenon, but rather a subjective experience that bears a variable relationship with tissue damage. The task of researchers and clinicians is to identify any factors that might contribute to the individual's pain experience. These could include somatic (physical) and psychological factors, as well as contextual factors, such as situational

and cultural considerations. Pain expression, which may include facial expressions, body posture, language, vocalizations, and avoidance behaviour, partially represents the complexity of the psychological experience, but is not equivalent to it (Crombez & Eccleston, 2002; Kunz et al, 2004; Vervoot et al, 2009). Engel's enunciation (Engel, 1977) of a biopsychosocial model of illness has provided a framework for considering pain phenomena. A dynamic engagement between the clinician and the patient was recommended in order to explore possible relevant biological, psychological, and socio-cultural contributions to the clinical problem at hand.

The biopsychosocial model of pain (Turk & Monarch, 1995) proposed that biological factors can influence physiological changes and that psychological factors are reflected in the appraisal and perception of internal physiological phenomena. These appraisals and behavioural responses are, in turn, influenced by social or environmental factors, such as reinforcement contingencies (eg Flor et al, 2002). At the same time, the model also proposes that psychological and social factors can influence biological factors, such as hormone production, activity in the autonomic nervous system and physical deconditioning. Experimental evidence supports these propositions (Flor & Hermann, 2004). Other concepts and models of pain which challenge traditional reductionist, mind-body or biomedical paradigms have also been promulgated (Quintner et al, 2008).

1.2.1 Psychological factors

Psychological factors that influence the experience of pain include the processes of attention, other cognitive processes (eg memory/learning, thought processing, beliefs, mood), behavioural responses, and interactions with the person's environment.

Attention

In relation to pain, attention is viewed as an active process and the primary mechanism by which nociception accesses awareness and disrupts current activity (Eccleston & Crombez, 1999).

The degree to which pain may interrupt attention depends on factors such as intensity, novelty, unpredictability, degree of awareness of bodily information, threat value of pain, catastrophic thinking, presence of emotional arousal, environmental demands (such as task difficulty), and emotional significance. Evidence from experimental studies has demonstrated that anxiety sensitivity (Keogh & Cochrane, 2002 **Level III-2**) and pain catastrophising (Vancleef & Peters, 2006 **Level III-2**) may also influence the interruptive qualities of pain on attention.

Learning and memory

The role of learning or memory has primarily been studied in laboratory settings with experimentally induced pain. A number of studies using healthy subjects have demonstrated that reports of pain (eg pain severity ratings) can be operantly conditioned by their consequences and this effect can be reflected in measures of associated skin conductance responses, facial activity and cortical responses (Flor et al, 2002; Jolliffe & Nicholas, 2004). Taken together, these studies provide support for the thesis that the experience of pain is not solely due to noxious input, but that environmental contingencies can also contribute.

Learning processes may also be involved in the development and maintenance of chronic pain (Birbaumer et al, 1995). Evidence of both classical and instrumental (operant) learning responses were reflected in stereotypy, or repetitive movements, of certain muscle groups to personally relevant stressful situations, as well as conditioning of muscle and pain responses to previously neutral tones and images.

Beliefs, thought processes

Empirical evidence supports a role for fear of pain contributing to the development of avoidance responses following pain and injury, which ultimately lead to disability in many

people with persisting pain (Leeuw et al, 2007). Negative appraisals of internal and external stimuli (eg catastrophising), negative affectivity and anxiety sensitivity could contribute to the development of pain-related fear and, in turn, lead to escape and avoidance behaviours, as well as hypervigilance to internal and external illness information, muscular reactivity, and physical disuse and behavioural changes.

1.2.2 Acute pain settings

The contribution of psychosocial factors to the pain experience is important in acute and chronic pain settings as well as in the transition from acute to chronic pain (Linton, 2000 **Level IV**; Pincus et al, 2002 **Level IV**).

Preoperative anxiety has been shown to be associated with higher pain intensities in the first hour after a variety of different operations (Kalkman et al, 2003 **Level IV**), including abdominal (Caumo et al, 2002 **Level IV**; Granot & Ferber, 2005 **Level IV**), coronary artery bypass (Nelson et al, 1998 **Level IV**), gynaecological (Hsu et al, 2005 **Level IV**; Carr et al, 2006 **Level IV**) and varicose vein (Terry et al, 2007 **Level IV**) surgery, and after laparoscopic tubal ligation (Rudin et al, 2008 **Level IV**). Preoperative anxiety was also associated with increased pain and reduced function 1 year after total knee replacement (Brander et al, 2003 **Level IV**), but not 5 years after the surgery (Brander et al, 2007 **Level IV**). Similarly, preoperative psychological distress was shown to predict pain up to 2 years after knee arthroplasty (Lingard & Riddle, 2007 **Level IV**). Pain from 2 to 30 days after breast surgery was also predicted by preoperative anxiety (Katz et al, 2005 **Level IV**). After elective Caesarean section, preoperative anxiety did not predict analgesic use, but was negatively associated with maternal satisfaction and speed of recovery (Hobson et al, 2006 **Level IV**).

In patients who underwent repair of their anterior cruciate ligament, those with high Pain Catastrophising Scale (PCS) scores, assessed prior to surgery, reported more pain immediately after surgery and when walking at 24 hours compared with those with low scores, but there was no difference in analgesic consumption (Pavlin et al, 2005 **Level IV**). After breast surgery, catastrophising was associated with increased pain intensity and analgesic use (Jacobsen & Butler, 1996 **Level IV**) and with higher pain scores after abdominal surgery (Granot & Ferber, 2005 **Level IV**) and Caesarean section (Strulov et al, 2007 **Level IV**). Preoperative PCS scores also predicted pain after knee arthroplasty on the second postoperative day (Roth et al, 2007 **Level IV**) and at 6 weeks (Sullivan et al, 2009 **Level IV**) and 2 years after surgery (Forsythe et al, 2008 **Level IV**).

Preoperative depression (Caumo et al, 2002 **Level IV**; Kudoh et al, 2002 **Level III-2**; Katz et al, 2005 **Level IV**; Rudin et al, 2008 **Level IV**) and neuroticism (Bisgaard et al, 2001 **Level IV**) were predictors of postoperative pain early after surgery; preoperative depression was also associated with pain 1 year after total knee replacement (Brander et al, 2003 **Level IV**) and reduced function at both 1 year (Brander et al, 2003 **Level IV**) and 5 years later (Brander et al, 2007 **Level IV**). Strong information-seeking behaviour was associated with a reduction in the incidence of severe pain (Kalkman et al, 2003 **Level IV**).

Preoperative anxiety and moderate to severe postoperative pain are, in turn, predictors of postoperative anxiety (Caumo et al, 2001 **Level IV**; Carr et al, 2006 **Level IV**).

In opioid-tolerant patients, the anxiety and autonomic arousal associated with withdrawal (Tetrault & O'Connor, 2008) may also impact on acute pain experience and report (see Section 11.7 for further details). Behavioural problems were more common in methadone-maintained patients who required inpatient acute pain management (Hines et al, 2008 **Level III-2**).

Patient-controlled analgesia

A number of studies have looked specifically at the relationship between pain relief and psychological factors in patients using patient-controlled analgesia (PCA) in the postoperative period.

In general, anxiety seems to be the most important psychological variable that affects PCA use. Preoperative anxiety correlated with increased postoperative pain intensity, the number of PCA demands made by the patient (often 'unsuccessful', that is, during the lockout interval), degree of dissatisfaction with PCA and lower self-reports of quality of analgesia (Jamison et al, 1993 **Level IV**; Perry et al, 1994 **Level IV**; Thomas et al, 1995 **Level III-1**; Brandner et al, 2002 **Level IV**; Ozalp et al, 2003 **Level IV**; Hsu et al, 2005 **Level IV**; De Cosmo et al, 2008 **Level IV**). Another study designed to look at predictors of PCA demands made during the lockout interval also found that anxiety and negative affect positively predicted PCA lockout interval demands and postoperative pain, as did preoperative intrusive thoughts and avoidant behaviours about the impending surgery (Katz et al, 2008 **Level IV**).

Evidence regarding PCA opioid consumption is contradictory; both no change (Gil et al, 1990 **Level IV**; Gil et al, 1992 **Level IV**; Jamison et al, 1993 **Level IV**) and an increase (Ozalp et al, 2003 **Level IV**; De Cosmo et al, 2008 **Level IV**; Katz et al, 2008 **Level IV**) have been reported.

In a study looking at the effect of a number of psychological factors on both pain and PCA morphine use in the immediate postoperative period and on pain 4 weeks after surgery, preoperative self-distraction coping positively predicted postoperative pain levels and morphine consumption; emotional support and religious-based coping positively predicted PCA morphine consumption; and preoperative distress, behavioural disengagement, emotional support, and religious-based coping also positively predicted pain levels 4 weeks after surgery (Cohen et al, 2005 **Level IV**).

There was no relationship between locus of control and postoperative pain intensity, satisfaction with PCA or PCA dose-demand ratio (Brandner et al, 2002 **Level IV**). However, preoperative depression was associated with increased pain intensity, opioid requirements, PCA demands and degree of dissatisfaction (Ozalp et al, 2003 **Level IV**; De Cosmo et al, 2008 **Level IV**).

Key messages

1. Preoperative anxiety, catastrophising, neuroticism and depression are associated with higher postoperative pain intensity (**U**) (**Level IV**).
2. Preoperative anxiety and depression are associated with an increased number of PCA demands and dissatisfaction with PCA (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

- Pain is an individual, multifactorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope (**U**).

1.3 PROGRESSION OF ACUTE TO CHRONIC PAIN

The importance of addressing the link between acute and chronic pain has been emphasised by recent studies. To highlight this link, chronic pain is increasingly referred to as persistent pain. A survey of the incidence of chronic pain-related disability in the community concluded

that patients often relate the onset of their pain to an acute injury, drawing attention to the need to prevent the progression from acute to chronic pain (Blyth et al, 2003 **Level IV**).

The association between acute and chronic pain is well-defined, but few randomised controlled studies have addressed the aetiology, time course, prevention or therapy of the transition between the two pain states. Acute pain states that may progress to chronic pain include postoperative and post-traumatic pain (see below and Section 9.1), acute back pain (see Section 9.4) and herpes zoster (see Section 9.6.2).

Chronic pain is common after surgery (see Table 1.2) (Kehlet et al, 2006; Macrae, 2008) and represents a significant source of ongoing disability, often with considerable economic consequences. Such pain frequently has a neuropathic element. For example, all patients with chronic postherniorrhaphy pain had features of neuropathic pain (Aasvang et al, 2008 **Level IV**). Neuropathic pain may be seen early in the postoperative period (see Section 9.1.1).

There is some evidence that specific early analgesic interventions may reduce the incidence of chronic pain after surgery. Epidural analgesia initiated prior to thoracotomy and continued into the postoperative period resulted in significantly fewer patients reporting pain 6 months later compared with patients who had received intravenous (IV) PCA opioids for postoperative analgesia (45% vs 78% respectively) (Senturk et al, 2002 **Level II**). There was no statistically significant difference in the incidence of chronic pain between patients given pre-emptive epidural analgesia (initiated prior to surgery) and patients in whom epidural analgesia was commenced after surgery – 39.6% vs 48.6% (Bong et al, 2005 **Level I**). In patients undergoing colonic resection, continuous perioperative epidural analgesia led to a lower risk of developing persistent pain up to 1 year after surgery compared with IV analgesia (Lavand'homme et al, 2005 **Level II**).

Spinal anaesthesia in comparison to general anaesthesia reduced the risk of chronic postsurgical pain after Caesarean section (Nikolajsen et al, 2004 **Level IV**) and hysterectomy (OR: 0.42; CI 0.21 to 0.85) (Brandsborg et al, 2007 **Level IV**). The latter study found no difference in risk between abdominal and vaginal hysterectomy.

An infusion of ropivacaine into the site of iliac crest bone graft harvest resulted in significantly less pain in the iliac crest during movement at 3 months (Blumenthal et al, 2005 **Level II**).

Local anaesthetic wound infiltration reduced the proportion of patients with persistent pain and neuropathic pain 2 months following intracranial tumour resection (Batoz et al, 2009 **Level II**).

Preincisional paravertebral block reduced prevalence and intensity of pain 12 months after breast surgery (Kairaluoma et al, 2006 **Level II**). Perioperative use of gabapentin or mexiletine after mastectomy reduced the incidence of neuropathic pain at 6 months postoperatively, from 25% in the placebo to 5% in both treatment groups (Fassoulaki et al, 2002 **Level II**). Similar protective results were achieved by the same group by the use of a eutectic mixture of local anaesthetics alone (Fassoulaki et al, 2000 **Level II**) or in combination with gabapentin (Fassoulaki et al, 2005 **Level II**).

Deliberate neurectomy (of the ilioinguinal nerve) for inguinal hernia repair reduced the incidence of chronic postsurgical pain (from 21% to 6%) (Malekpour et al, 2008 **Level II**), although this was not seen in an earlier study (Picchio et al, 2004 **Level II**).

See Section 1.5 below for more examples of the use of pre-emptive and preventive analgesic interventions in attempts to reduce the risk of persistent pain after surgery, and Sections 9.1.2 to 9.1.3 for more details on prevention of phantom pain after limb amputation and other postoperative pain syndromes.

Table 1.2 Incidence of chronic pain after surgery

Type of operation	Incidence of chronic pain (%)	Estimated incidence of chronic severe pain [>5 out of 10/10] (%)
Amputation	30–85	5–10
Thoracotomy	5–65	10
Mastectomy	11–57	5–10
Inguinal hernia	5–63	2–4
Coronary bypass	30–50	5–10
Caesarean section	6–55	4
Cholecystectomy	3–50	Not estimated
Vasectomy	0–37	Not estimated
Dental surgery	5–13	Not estimated

Sources: Adapted from Kehlet et al (Kehlet et al, 2006) and Macrae (Macrae, 2008)

1.3.1 Predictive factors for chronic postsurgical pain

A number of risk factors for the development of chronic postsurgical pain have been identified (Kehlet et al, 2006; Macrae, 2008). A systematic review of psychosocial factors identified depression, psychological vulnerability, stress and late return to work as having a correlation to chronic postsurgical pain (Hinrichs-Rocker et al, 2009 **Level III-3**). Very young age may be a protective factor as hernia repair in children under 3 months age did not lead to chronic pain in adulthood (Aasvang & Kehlet, 2007 **Level IV**).

Table 1.3 Risk factors for chronic postsurgical pain

Preoperative factors	Pain, moderate to severe, lasting more than 1 month Repeat surgery Psychologic vulnerability (eg catastrophising) Preoperative anxiety Female gender Younger age (adults) Workers' compensation Genetic predisposition Inefficient diffuse noxious inhibitory control (DNIC)
Intraoperative factors	Surgical approach with risk of nerve damage
Postoperative factors	Pain (acute, moderate to severe) Radiation therapy to area Neurotoxic chemotherapy Depression Psychological vulnerability Neuroticism Anxiety

Sources: Adapted from Kehlet et al (Kehlet et al, 2006) and Macrae (Macrae, 2008)

1.3.2 Mechanisms for the progression from acute to chronic pain

The pathophysiological processes that occur after tissue or nerve injury mean that acute pain may become persistent (Cousins et al, 2000). Such processes include inflammation at the site of tissue damage with a barrage of afferent nociceptor activity that produces changes in the peripheral nerves, spinal cord, higher central pain pathways and the sympathetic nervous system (see Section 1.1).

After limb amputation, reorganisation or remapping of the somatosensory cortex and other cortical structures may be a contributory mechanism in the development of phantom limb pain (Flor et al, 1995; Grusser et al, 2004). There is preclinical and clinical evidence of a genetic predisposition for chronic pain (Mogil, 1999), although one study found that an inherited component did not feature in the development of phantom pain in members of the same family who all had a limb amputation (Schott, 1986).

Descending pathways of pain control may be another relevant factor as patients with efficient diffuse noxious inhibitory control (DNIC) had a reduced risk of developing chronic postsurgical pain (Yarnitsky et al, 2008 **Level III-2**).

Key messages

1. Some specific early anaesthetic and/or analgesic interventions reduce the incidence of chronic pain after surgery (**S**) (**Level II**).
2. Chronic postsurgical pain is common and may lead to significant disability (**U**) (**Level IV**).
3. Risk factors that predispose to the development of chronic postsurgical pain include the severity of pre- and postoperative pain, intraoperative nerve injury and psychosocial factors (**U**) (**Level IV**).
4. All patients with chronic postherniorrhaphy pain had features of neuropathic pain (**N**) (**Level IV**).
5. Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Caesarean section (**N**) (**Level IV**).

1.4 PRE-EMPTIVE AND PREVENTIVE ANALGESIA

In laboratory studies, administration of an analgesic prior to an acute pain stimulus more effectively minimises dorsal horn changes associated with central sensitisation than the same analgesic given after the pain state is established (see Section 1.1) (Woolf, 1983). This led to the hypothesis that pain relief prior to surgery may enhance postoperative pain management – that is, ‘pre-emptive preoperative analgesia’ (Wall, 1988). However, individual clinical studies have reported conflicting outcomes when comparing ‘preincisional’ with ‘postincisional’ interventions. In part this relates to variability in definitions, deficiencies in clinical trial design and differences in the outcomes available to laboratory and clinical investigators (Kissin, 1994; Katz & McCartney, 2002).

As the process of central sensitisation relates not only to skin incision but also to the extent of intraoperative tissue injury and postoperative inflammation, the focus has shifted from

the timing of a single intervention to the concept of ‘protective’ and therefore ‘preventive’ analgesia (Kissin, 1994) (see Table 1.4). The differences in these terms relates to the outcomes being described, because all rely on minimising sensitisation. *Pre-emptive* analgesia has been described above and is measured in terms of pain intensity or related outcomes. *Protective* analgesia describes a technique that reduces measures of sensitisation such as hyperalgesia. *Preventive* analgesia is the persistence of analgesic treatment efficacy beyond its expected duration. In clinical practice, preventive analgesia appears to be the most relevant and holds the most hope for minimising chronic pain after surgery or trauma, possibly because it decreases central sensitisation and ‘windup’. An important consideration to maximise the benefit of any preventive strategy is that the active intervention should be continued for as long as the sensitising stimulus persists, that is well into the postoperative period (Dahl & Moiniche, 2004; Pogatzki-Zahn & Zahn, 2006).

Table 1.4 Definitions of pre-emptive and preventive analgesia

Pre-emptive analgesia	Preoperative treatment is more effective than the identical treatment administered after incision or surgery. The only difference is the timing of administration.
Preventive analgesia	Postoperative pain and/or analgesic consumption is reduced relative to another treatment, a placebo treatment, or no treatment as long as the effect is observed at a point in time that exceeds the expected duration of action of the intervention. The intervention may or may not be initiated before surgery.

Sources: Moiniche et al (Moiniche et al, 2002) and Katz & McCartney (Katz & McCartney, 2002).

The benefits of pre-emptive analgesia have been questioned by two systematic reviews (Dahl & Moiniche, 2004; Moiniche et al, 2002). However a more recent meta-analysis provided support for pre-emptive epidural analgesia (Ong et al, 2005 **Level I¹**). The efficacy of different pre-emptive analgesic interventions (epidural analgesia, local anaesthetic wound infiltration, systemic NMDA antagonists, systemic opioids, and systemic NSAIDs) was analysed in relation to different analgesic outcomes (pain intensity scores, supplemental analgesic consumption, time to first analgesic). The effect size was most marked for epidural analgesia (0.38; CI 0.28 to 0.47) and improvements were found in all outcomes. Pre-emptive effects of local anaesthetic wound infiltration and NSAID administration were also found, but results were equivocal for systemic NMDA antagonists and there was no clear evidence for a pre-emptive effect of opioids.

Note: reversal of conclusions

This reverses the Level 1 conclusion in the previous edition of this document as pre-emptive effects have been shown with epidural analgesia; earlier meta-analyses using more simple outcomes had reported no pre-emptive effects.

Pre-emptive thoracic epidural analgesia (local anaesthetic +/- opioid) reduced the severity of acute pain only on coughing following thoracotomy. There was a marginal effect on pain at rest and, although acute pain was a predictor of chronic pain at 6 months in two studies, there was no statistically significant difference in the incidence of chronic pain in the pre-emptive

1 This meta-analysis includes studies that have since been withdrawn from publication. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles. After excluding results obtained from the retracted publications, Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data relating to possible pre-emptive effects of local anaesthetic wound infiltration and NSAID administration. They concluded that removal of this information did not significantly alter the results of the meta-analysis.

(epidural analgesia initiated prior to surgery) versus control (epidural analgesia initiated after surgery) — 39.6% vs 48.6% (Bong et al, 2005 **Level I**).

A systematic review (Katz & Clarke, 2008 **Level I**²) reported preventive effects following the use of a number of different drugs, but equivocal or no benefit from pre-emptive treatment (Table 1.5). The methodology was unable to identify specific therapeutic techniques that may be of benefit.

Table 1.5 Summary of studies according to target agent administered

Agent(s)	No. of studies	Pre-emptive effects		Preventive effects		Opposite effects	Total no. effects
		Positive	Negative	Positive	Negative		
Gabapentin	6	0 (0)	1 (16.7)	4 (66.6)	1 (16.7)	0 (0)	6 (100)
Local anaesthetics	13	3 (20)	3 (20)	6 (40)	1 (6.7)	2 (13.3)	15 (100)
Opioids	5	3 (60)	1 (20)	0 (0)	1 (20)	0 (0)	5 (100)
	[-1]	[-1]					[-1]
NSAIDs	14	7 (43.8)	3 (18.8)	4 (25)	2 (12.4)	0 (0)	16 (100)
	[-2]	[-1]		[-1]			[-2]
NMDA antagonists	14	2 (11.8)	1 (5.9)	9 (53)	4 (23.4)	1 (5.9)	17 (100)
Multimodal	5	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	0 (0)	6 (100)
Other	4	1 (25)	0 (0)	3 (75)	0 (0)	0 (0)	4 (100)
	[-1]			[-1]			[-1]
Total^a	61	17^b	10	28^c	11	3	69
		(24.6)	(14.5)	(40.6)	(15.9)	(4.4)	(100)

Notes: Table shows the total number of studies and number (%) with positive and negative pre-emptive and preventive effects. Also shown is the number (%) of studies reporting effects opposite to those predicted and the total number of effects (positive, negative and opposite). The total number of effects exceeds the number of studies because some studies were designed to evaluate both pre-emptive and preventive effects. See text for definition of pre-emptive and preventive effects.

a $p = 0.02$ for z-test comparison of proportion of total positive pre-emptive plus preventive effects (0.64) versus proportion of total negative pre-emptive plus preventive effects (0.31).

b $p = 0.36$ for z-test comparison of proportion of total positive pre-emptive effects ($17/27 = 0.63$) versus proportion of total negative pre-emptive effects ($10/27 = 0.37$)

c $p = 0.03$ for z-test comparison of proportion of total positive preventive effects ($28/39 = 0.72$) versus proportion of total negative preventive effects ($11/39 = 0.28$)

Legend: NSAIDs: non-steroidal anti-inflammatory drugs; NMDA: N-methyl-D-aspartate

Source: Reproduced with kind permission from Katz and Clark, Preventive analgesia and beyond: current status, evidence, and future directions, Table 9.4 p 165 *Clinical Pain Management: Acute Pain 2e*, Hodder Arnold.

2 This meta-analysis includes studies that have since been withdrawn from publication and which are shown as subtractions in Table 1.5. These were four positive reports: pre-emptive effects of opioids, pre-emptive effects of venlafaxine (listed under 'Other'), and both pre-emptive and preventive effects of NSAIDs. Reanalysis of the data would be required to determine the overall strength of the evidence. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles.

As activation of the NMDA receptor plays an important role in central sensitisation, many studies have focussed on the ability of NMDA receptor antagonists to produce pre-emptive or preventive analgesic effects. A qualitative systematic review of NMDA receptor antagonists showed that ketamine and dextromethorphan produced a significant preventive analgesic benefit; in all positive preventive studies, a direct analgesic benefit of the drug also occurred in the early postoperative period; no positive effect was seen in four studies using magnesium (McCartney et al, 2004 **Level I**). The addition of low-dose IV ketamine to thoracic epidural analgesia reduced the severity and need for treatment of post-thoracotomy pain at 1 and 3 months postoperatively (Suzuki et al, 2006 **Level II**). However, in a later study of thoracic surgery patients, when single dose intrapleural ropivacaine and intravenous analgesia was combined with either perioperative ketamine or saline, no difference in chronic pain up to 4 months was noted (Duale et al, 2009 **Level II**).

In a study of multimodal analgesia (local anaesthetic, opioid, ketamine and clonidine) in four groups of patients having colonic resection, a clear preventive effect on the development of residual pain up to 1 year after surgery was demonstrated with continuous perioperative epidural analgesia; residual pain at 1 year was lowest in patients who received intraoperative versus postoperative epidural analgesia (Lavand'homme et al, 2005 **Level II**).

Key messages

1. The timing of a single analgesic intervention (preincisional rather than postincisional), defined as pre-emptive analgesia, has a significant effect on postoperative pain relief with epidural analgesia (**R**) (**Level I**).
2. There is evidence that some analgesic interventions have an effect on postoperative pain and/or analgesic consumption that exceeds the expected duration of action of the drug, defined as preventive analgesia (**U**) (**Level I**).
3. NMDA receptor antagonist drugs in particular show preventive analgesic effects (**U**) (**Level I**).
4. Perioperative epidural analgesia combined with ketamine intravenously decreases hyperalgesia and long-term pain up to 1 year after colonic surgery compared with intravenous analgesia alone (**N**) (**Level II**).

1.5 ADVERSE PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF ACUTE PAIN

1.5.1 Acute pain and the injury response

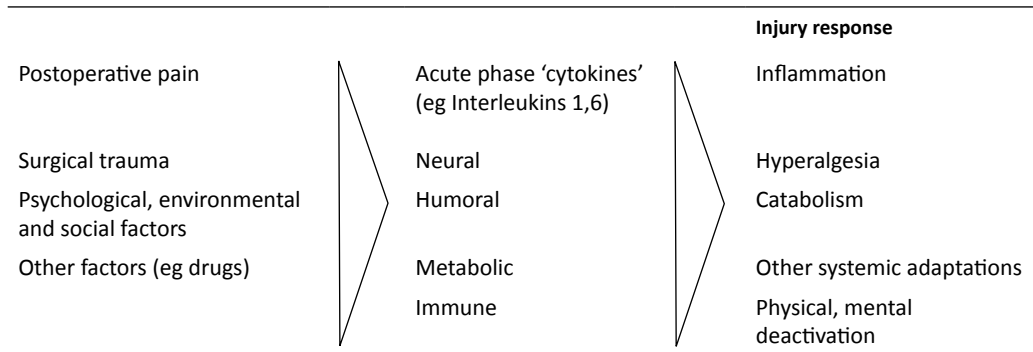
Acute pain is one of the activators of the complex neurohumoral and immune response to injury (Figure 1.2), and both peripheral and central injury responses have a major influence on acute pain mechanisms. Thus acute pain and injury of various types are inevitably interrelated and if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome (Kehlet & Dahl, 2003; Chapman et al, 2008).

Although published data relate to the *combination* of surgery or trauma and the associated acute pain, some data have been obtained with experimental pain in the absence of injury. Electrical stimulation of the abdominal wall results in a painful experience (visual analogue scale [VAS] 8/10) and an associated hormonal/metabolic response, which includes increased cortisol, catecholamines and glucagon, and a decrease in insulin sensitivity (Greisen et al, 2001). Although acute pain is only one of the important triggers of the 'injury response' (Figure 1.2),

as the magnitude and duration of the response is related to the magnitude and duration of the stimulus, effective pain relief can have a significant impact on the injury response (Liu & Wu, 2008; Carli & Schricker, 2009).

Release of proinflammatory cytokines may contribute to postoperative ileus, but the impact of modulating this response on overall patient outcome requires further evaluation. Intravenous lignocaine infusion attenuated postoperative increases in pro-inflammatory cytokines, such as IL-6 (interleukin-6), IL-8 and IL-1RA (a competitive inhibitor of IL-1 β) and was associated with more rapid return of bowel function following abdominal surgery (Kuo et al, 2006 **Level II**; Herroeder et al, 2007 **Level II**). Reductions in pain scores and opioid consumption were found in only one study (Kuo et al, 2006 **Level II**). Benefits of lignocaine were more marked when administered via the thoracic epidural route than by intravenous infusion (Kuo et al, 2006 **Level II**).

Figure 1.2 The injury response



Note: Pain is only one of the factors, including psychological and environmental factors, that trigger complex intermediates (neural, humoral etc) leading to the 'injury response'. Thus acute pain and the injury response are inevitably inter-related. The end result is physical and mental deactivation.

Source: *Acute Pain Management: the Scientific Evidence* (NHMRC 1999); © Commonwealth of Australia, reproduced with permission.

1.5.2 Adverse physiological effects

Clinically significant injury responses can be broadly classified as inflammation, hyperalgesia, hyperglycaemia, protein catabolism, increased free fatty acid levels (lipolysis) and changes in water and electrolyte flux (Liu & Wu, 2008; Carli & Schricker, 2009) (Figure 1.3). In addition, there are cardiovascular effects of increased sympathetic activity and diverse effects on respiration, coagulation and immune function (Liu & Wu, 2008).

Table 1.6 Metabolic and endocrine responses to injury

Endocrine	↑ Catabolic hormones	↑ ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagons, IL-1, TNF, IL-6
	↓ Anabolic hormones	↓ Insulin, testosterone
Metabolic		
<i>carbohydrate</i>	Hyperglycaemia, glucose intolerance, insulin resistance	↑ Glycogenolysis, gluconeogenesis (cortisol, glucagon, growth hormone, adrenaline, free fatty acids) ↓ Insulin secretion/activation
<i>protein</i>	Muscle protein catabolism, ↑ synthesis of acute phase proteins	↑ Cortisol, adrenaline, glucagons, IL-1, IL-6, TNF
<i>lipid</i>	↑ Lipolysis and oxidation	↑ Catecholamines, cortisol, glucagon, growth hormone
Water and electrolyte flux	Retention of water and sodium, ↑ excretion of potassium and ↓ functional ECF with shifts to ICF	↑ Catecholamine, aldosterone, ADH, cortisol, angiotensin II, prostaglandins and other factors

Note: ACTH: adrenocorticotrophic hormone; ADH: antidiuretic hormone; ECF: extracellular fluid; ICF: intracellular fluid; IL: interleukin; TNF: tumour necrosis factor.

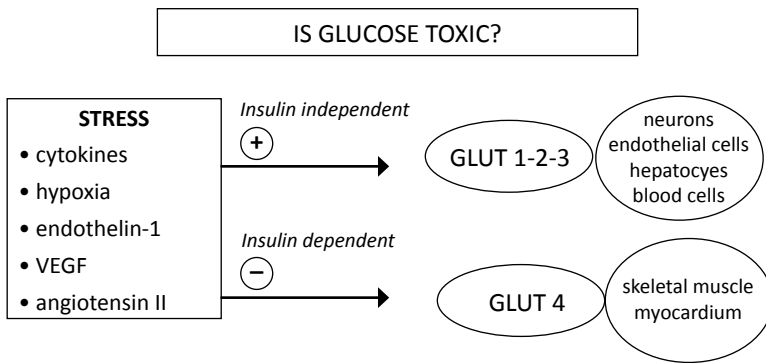
Source: *Acute Pain Management: the Scientific Evidence* (NHMRC 1999); copyright Commonwealth of Australia, reproduced with permission.

Hyperglycaemia

Hyperglycaemia is broadly proportional to the extent of the injury response. Injury response mediators stimulate insulin-independent membrane glucose transporters glut-1, 2 and 3, which are located diversely in brain, vascular endothelium, liver and some blood cells. Circulating glucose enters cells that do not require insulin for uptake, resulting in cellular glucose overload and diverse toxic effects. Excess intracellular glucose non-enzymatically glycosylates proteins such as immunoglobulins, rendering them dysfunctional. Alternatively, excess glucose enters glycolysis and oxidative phosphorylation pathways, leading to excess superoxide molecules that bind to nitric oxide (NO), with formation of peroxynitrate, ultimately resulting in mitochondrial dysfunction and death of cells served by glut-1, 2 and 3. Myocardium and skeletal muscle are protected from this toxicity because these two tissues are served by glut-4, the expression of which is inhibited by injury response mediators (Figure 1.3) (Carli & Schricker, 2009).

Even modest increases in blood glucose can be associated with poor outcome particularly in metabolically challenged patients such as people with diabetes (Lugli et al, 2008 **Level II**). Fasting glucose levels over 7 mmol/L or random levels of greater than 11.1 mmol/L were associated with increased in-hospital mortality, a longer length of stay and higher risk of infection in intensive care patients (Van den Berghe, 2004). Tight glycaemic control has been associated with improved outcomes following coronary artery bypass graft (CABG) in patients with diabetes (Lazar et al, 2004 **Level II**), but the risks and benefits of tight glycaemic control in intensive care patients (Wiener et al, 2008 **Level I**) continues to be debated (Fahy et al, 2009 **Level IV**).

Figure 1.3 Proposed pathways of glucose-induced cellular toxicity



Note: VEGF=vascular endothelial growth factor

Source: Reproduced with kind permission from Carli and Schricker, Modification of Metabolic Response to Surgery by Neural Blockade, Figure 6.3 page 134 *Neural Blockade in Clinical Anesthesia and Pain Medicine 4th Ed*, Wolters Kluwer, Lippincott Williams & Wilkins.

Lipotoxicity

Free fatty acid (FFA) levels are increased due to several factors associated with the injury response and its treatment (see Table 1.6) and can have detrimental effects on cardiac function. High levels of FFA can depress myocardial contractility (Korvald et al, 2000), increase myocardial oxygen consumption (without increased work) (Oliver & Opie, 1994; Liu et al, 2002), and impair calcium homeostasis and increase free radical production leading to electrical instability and ventricular arrhythmias (Oliver & Opie, 1994).

Protein catabolism

The injury response is associated with an accelerated protein breakdown and amino acid oxidation, in the face of insufficient increase in protein synthesis. Following abdominal surgery, amino acid oxidation and release from muscle increased by 90% and 30% respectively, while whole body protein synthesis increased only 10% (Harrison et al, 1989 **Level IV**). After cholecystectomy 50 g of nitrogen may be lost (1 g nitrogen = 30 g lean tissue) which is equivalent to 1500 g of lean tissue. Importantly, the length of time for return of normal physical function after hospital discharge has been related to the total loss of lean tissue during hospital stay (Chandra, 1983).

Protein represents both structural and functional body components, thus loss of lean tissue may lead to delayed wound healing (Windsor & Hill, 1988 **Level III-3**), reduced immune function (Chandra, 1983) and diminished muscle strength (Watters et al, 1993 **Level III-3**) — all of which may contribute to prolonged recovery and increased morbidity (Watters et al, 1993; Christensen et al, 1982).

An overall reduced ability to carry out activities of daily living (ADLs) results from muscle fatigue and muscle weakness. Impaired nutritional intake, inflammatory–metabolic responses, immobilisation, and a subjective feeling of fatigue may all contribute to muscle weakness (Christensen et al, 1990). Such effects are broadly proportional to the extent of injury but there are major variations across populations, with durations also varying up to 3 to 4 weeks.

1.5.3 Pain and analgesia: effects on injury-induced organ dysfunction

Pain from injury sites can activate sympathetic efferent nerves and increase heart rate, inotropy, and blood pressure. As sympathetic activation increases myocardial oxygen demand and reduces myocardial oxygen supply, the risk of cardiac ischaemia, particularly in patients with pre-existing cardiac disease, is increased. Enhanced sympathetic activity can also reduce gastrointestinal (GI) motility and contribute to ileus. Severe pain after upper abdominal and thoracic surgery contributes to an inability to cough and a reduction in functional residual capacity, resulting in atelectasis and ventilation-perfusion abnormalities, hypoxaemia and an increased incidence of pulmonary complications. The injury response also contributes to a suppression of cellular and humoral immune function and a hypercoagulable state following surgery, both of which can contribute to postoperative complications. Patients at greatest risk of adverse outcomes from unrelieved acute pain include very young or elderly patients, those with concurrent medical illnesses and those undergoing major surgery (Liu & Wu, 2008).

All relevant studies address the combination of injury and pain. The majority involve use of epidural neural blockade, which in addition to effects on pain *per se* can influence the injury response (eg via reduced sympathetic activity). As a result, the site of epidural placement and extent of block can influence results. The impact of analgesic technique on outcome is more fully discussed in Section 7. Epidural analgesia has been reported to improve pain and decrease arrhythmias following cardiac surgery (Liu et al, 2004 **Level I**), but early reports of reduced postoperative myocardial infarction (Beattie et al, 2001 **Level I**) and impact on mortality have not been replicated (Rigg et al, 2002 **Level II**; Liu et al, 2004 **Level I**). Regional versus systemic analgesia decreased postoperative pulmonary complications (Rodgers et al, 2000 **Level I**; Ballantyne et al, 1998 **Level I**; Jorgensen et al, 2000 **Level I**) but the impact was greater following abdominal (Nishimori et al, 2006 **Level I**) than hip or knee surgery (Choi et al, 2003 **Level I**). Intraoperative epidural analgesia/anaesthesia (versus general anaesthesia) decreased the odds ratio for deep vein thrombosis (DVT) and postoperative confusion, but did not reduce mortality following hip fracture (Parker et al, 2004 **Level I**). Epidural local anaesthetic, when compared to epidural or systemic opioid, enhanced return of GI function (Jorgensen et al, 2000 **Level I**). Compared with systemic opioid administration, intraoperative thoracic epidural anaesthesia also led to lower plasma concentrations of adrenaline (epinephrine) and cortisol, and prevented perioperative impairment of proinflammatory lymphocyte function (Ahlers et al, 2008 **Level II**). The advantages of epidural analgesia were greatest when used as part of a multimodal, accelerated rehabilitation care pathway, since other factors may influence GI recovery (Joshi, 2005).

There is also some evidence that regional anaesthetic and analgesic techniques might have a beneficial effect on rates of cancer recurrence after tumour resection. Paravertebral anaesthesia/analgesia reduced the risk of recurrence or metastases following mastectomy from 23% to 6% compared with general anaesthesia and systemic morphine analgesia (Exadaktylos et al, 2006 **Level IV**). Similarly, after prostatectomy under general anaesthesia, epidural analgesia compared with systemic morphine reduced the risk of recurrence by 57% (Biki et al, 2008 **Level IV**).

1.5.4 Acute rehabilitation and ‘fast-track’ surgery

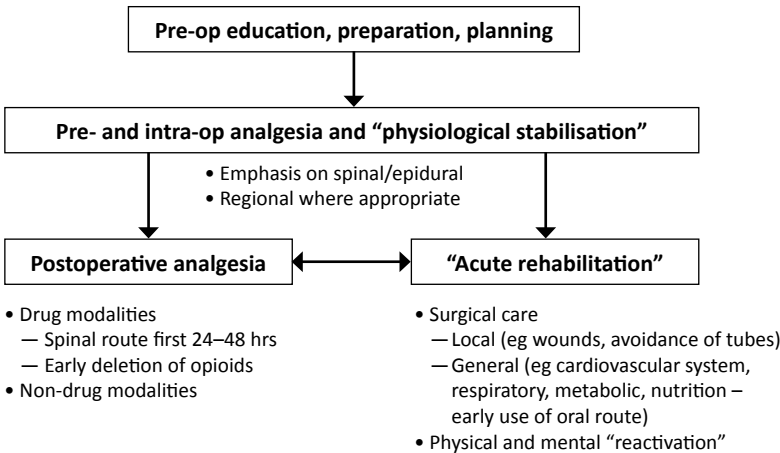
In view of the numerous triggers of the injury response, including acute nociception and pain, it is not surprising that early attempts to modify the catabolism of the injury response, with *pain relief alone*, were not successful. Following abdominal surgery, epidural analgesia without nutritional support had no effect on protein catabolism and related outcomes (Hjortso et al, 1985 **Level II**). Minimising the impact of perioperative fasting with IV amino acid infusions decreased postoperative protein catabolism following colorectal surgery (Schricker et al, 2008 **Level III-2**; Donatelli et al, 2006 **Level III-2**).

Epidural analgesia, aimed at the operative area spinal segments and comprising low doses of local anaesthetic and opioid, facilitated mobilisation and accelerated food intake. Such a program permitted a more rapid postoperative return of normal cardiopulmonary response to treadmill exercise and facilitated return of overall exercise capacity 6 weeks after surgery (Basse et al, 2002 **Level III-2**; Carli et al, 2002 **Level II**).

It can be seen from the foregoing that a multi-interventional and rehabilitation strategy is required, including very effective pain relief, if optimal outcomes are to be achieved, as outlined in procedure-specific recommendations from the PROSPECT group (Kehlet et al, 2007). Postoperative rehabilitation should include pharmacological, physical, psychological and nutritional components (Figure 1.4).

Recognition of the importance of the above factors has led to the concept of ‘fast-track’ surgery (Wilmore & Kehlet, 2001; White et al, 2007). This has provided enhanced recovery leading to decreased hospital stay with an apparent reduction in medical morbidity (Kehlet & Wilmore, 2008). For example, ‘fast-track’ colorectal programs have led to a reduction in length of hospital stay (Delaney et al, 2003 **Level II**; Jakobsen et al, 2006 **Level III-2**; Wind et al, 2006 **Level III-1**; Khoo et al, 2007 **Level II**); readmission rates may (Khoo et al, 2007 **Level II**; Jakobsen et al, 2006 **Level III-2**) or may not (Wind et al, 2006 **Level III-1**) be higher. A fast-track system also enabled early discharge (less than 3 days) after total hip and knee arthroplasty, although after total knee arthroplasty, pain at 10 days after discharge was still significant (52% of patients with moderate pain and 16% with severe pain) indicating a need for improved postdischarge analgesia (Andersen et al, 2009 **Level III-3**).

Figure 1.4 Acute pain management and rehabilitation



Source: Reproduced with kind permission from Carli and Schricker, Modification of Metabolic Response to Surgery by Neural Blockade, Figure 6.12 page 141 *Neural Blockade in Clinical Anesthesia and Pain Medicine, 4th Ed*, Wolters Kluwer, Lippincott Williams & Wilkins .

1.5.5 Adverse psychological effects

Psychological changes associated with acute pain have received less attention than those associated with chronic pain, however they are no less important. Sustained acute nociceptive input, as occurs after surgery, trauma or burns, can also have a major influence on psychological function, which may in turn alter pain perception. Failure to relieve acute pain may result in increasing anxiety, inability to sleep, demoralisation, a feeling of helplessness, loss of control, inability to think and interact with others — in the most extreme situations, where patients can no longer communicate, effectively they have lost their autonomy (Cousins et al, 2004). In some forms of acute pain (eg low back pain), psychological and environmental responses in the acute phase may be major determinants of progression to a persistent phase (Young Casey et al, 2008).

In acute pain, attention has been focussed on postoperative cognitive dysfunction (POCD). Although the aetiology of POCD is unknown, factors probably include dysregulation of cerebral neurotransmitters, patient factors (age, comorbidities, preoperative cognitive function and general health) (Newman et al, 2007; Monk et al, 2008), surgical procedures (eg coronary artery bypass) and perioperative drug therapy (Flacker & Lipsitz, 1999). Elderly patients have an increased incidence of POCD and are more likely to have prolonged symptoms (see Section 11.2.3). Neurotransmitters involved may include acetylcholine and serotonin and inflammatory mediators (eg cytokines) may also contribute, especially in the elderly (Caza et al, 2008). POCD after cardiac surgery may also be due in part to cerebral microembolism, global cerebral hypoperfusion, cerebral temperature perturbations, cerebral oedema, and possible blood-brain barrier dysfunction (Flacker & Lipsitz, 1999; Gao et al, 2005).

Key messages

1. Recognition of the importance of postoperative rehabilitation including pharmacological, physical, psychological and nutritional components has led to enhanced recovery (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion.

- Acute pain and injury of various types are inevitably interrelated and if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome (**U**).

1.6 PHARMACOGENOMICS AND ACUTE PAIN

An increasing number of genetic variants modulating nociception, susceptibility to pain conditions, as well as response to pharmacotherapy have been discovered.

Pharmacogenomics deals with the influence of genetic variation on drug response in patients. By correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity, the aim is to develop rational means to optimise drug therapy with respect to the patient's genotype and ensure maximum efficacy with minimal adverse effects. For example, genetic factors regulating opioid pharmacokinetics (metabolising enzymes, transporters) and pharmacodynamics (receptors and signal transduction elements) contribute to the large inter-patient variability in postoperative opioid requirements (Anderson & Palmer, 2006). Information from genotyping may help in selecting the analgesic drug and the dosing regimen for an individual patient (Lotsch & Geisslinger, 2006). Although there is currently limited information, often from small numbers of subjects, for translation into clinical practice (Stamer & Stuber,

2007; Anderson & Palmer, 2006), some preliminary estimates for dose adaptations are possible (Lotsch & Geisslinger, 2006). However, genetic factors must be considered within the context of the multiple interacting physiological, psychological and environmental factors that influence responses to pain and analgesia (Kim et al, 2009; Searle & Hopkins, 2009).

1.6.1 Loss of pain sensation

Recognised hereditary syndromes associated with loss of pain sensation include the 'channelopathy-associated insensitivity to pain' caused by variants in the SCN9A gene, which codes for the alpha-subunit of the voltage-gated sodium channel Na(v)1.7. Na(v)1.7 is located in peripheral neurons and plays an important role in action potential production in these cells. Mutations result in loss of Na(v)1.7 function and affected individuals are unable to feel physical pain (Drenth & Waxman, 2007).

Hereditary sensory and autonomic neuropathy (HSAN) I-V syndromes are associated with a range of genetic abnormalities and produce varying patterns of sensory and autonomic dysfunction and peripheral neuropathy (Oertel & Lotsch, 2008). Hereditary sensory neuropathy type I (HSN-I) is a dominantly transmitted sensorimotor axonal neuropathy accompanied by painless injuries. Hereditary sensory neuropathy type II (HSN-2) variants result in loss of sensitivity to touch, pain and temperature (Drenth & Waxman, 2007). Familial dysautonomia is a congenital sensory and autonomic neuropathy (HSN-3) that affects the development and survival of sensory, sympathetic, and some parasympathetic neurons and results in an indifference to pain and temperature. Hereditary sensory and autonomic neuropathy type IV (HSAN-4) is a severe autosomal recessive disorder characterised by childhood onset of insensitivity to pain and anhidrosis. HSAN-4 is caused by mutations in the NTRK1 gene coding for the tyrosine kinase receptor A (Wieczorek et al, 2008). HSAN type V is a very rare disorder. It is characterised by the absence of thermal and mechanical pain perception caused by a decreased number of small diameter neurons in peripheral nerves (de Andrade et al, 2008).

1.6.2 Reduced sensitivity to pain

Reduced pain sensitivity has been associated with variants in genes encoding the mu-opioid receptor (OPRM1), catechol-O-methyltransferase (COMT), guanosine triphosphate cyclohydrolase 1/dopa-responsive dystonia (GCH1), transient receptor potential (TRPV₁), and the melanocortin-1 receptor (MC1R) (Lotsch et al, 2006).

The mu-opioid receptor variant N40D which is coded by the single nucleotide polymorphism (SNP) 118A > G of the OPRM1 gene has been associated with reduced acute pain responsiveness (Fillingim et al, 2005 **Level III-3**; Lotsch et al, 2006 **Level IV**) but increased exogenous opioid analgesic requirements (Klepstad et al, 2004 **Level III-3**). Intrathecal fentanyl requirements in labour were reduced in women with the 304G allele but increased in those with the 304A allele of OPRM1 (Landau et al, 2008 **Level III-3**). For additional detail related to individual opioids see Section 4.1.2.

COMT metabolises noradrenaline, adrenaline, and dopamine, and has recently been implicated in the modulation of pain. COMT inhibition may lead to increased pain sensitivity via beta-adrenergic receptor dependent mechanisms (Nackley et al, 2007). Haplotypes with high COMT activity are associated with low pain sensitivity to mechanical and thermal stimuli (Diatchenko et al, 2005). The Val158Met polymorphism influences the activity of the COMT enzyme. In cancer pain, carriers of COMT Val/Val and Val/Met genotypes had higher morphine requirements than carriers of the Met/Met genotype (Reyes-Gibby et al, 2007 **Level III-3**).

GCH1 is the rate-limiting enzyme for tetrahydrobiopterin (BH₄) synthesis, an essential cofactor in the biosynthesis of biogenic amines and nitric oxide. It is a key modulator of peripheral

neuropathic and inflammatory pain (Montagna, 2007). A haplotype of the GCH1 gene present in 15.4% of humans has been associated with reduced sensitivity to pain following discectomy (Tegeader et al, 2006 **Level III-2**) and homozygotes have reduced sensitivity to experimental pain (Tegeader et al, 2008 **Level III-2**).

Point mutations affecting TRPV₁ were found in a person with total insensitivity to capsaicin (Park et al, 2007). Polymorphisms in the human TRPV₁ gene have been identified, but there has been no systematic investigation of their functional consequences (Xu et al, 2007).

Kappa-opioid agonists such as nalbuphine and pentazocine have greater analgesic efficacy in women than in men (Gear et al, 1996 **Level III-3**; Gear et al, 1999 **Level II**). Subjects carrying loss-of-function melanocortin-1 receptor gene (MC1R) variants possess a red-hair fair-skin phenotype (Oertel & Lotsch, 2008). There was a significantly greater analgesic effect from a kappa-opioid agonist in female subjects with two variant (non-functional) alleles of the MC1R gene compared with those with zero or one allele (Mogil et al, 2003 **Level III-3**). Subject with non-functional alleles also had reduced sensitivity to noxious stimuli and an increased analgesic response to morphine-6-glucuronide (Mogil et al, 2005 **Level III-3**).

1.6.3 Drug metabolism

Drug-metabolising enzymes represent a major target for identifying associations between an individual's genetic profile and drug response (pharmacogenetics) (Stamer & Stuber, 2007). The polymorphic cytochrome P450 enzymes metabolise numerous drugs and show inter-individual variability in their catalytic activity. The CYP2D6 gene is highly polymorphic (Stamer & Stuber, 2007) and is of clinical interest as it influences the metabolism of codeine, dihydrocodeine, oxycodone and tramadol to the more potent hydroxyl metabolites, which have a higher affinity for the mu-opioid receptor (Anderson & Palmer, 2006; Mikus & Weiss, 2005).

Over 100 allelic variants of CYP2D6 have been identified, resulting in wide variability in function. Individuals carrying two wild type alleles display normal enzyme activity and are known as extensive metabolisers; intermediate metabolisers are heterozygotes with two variant alleles known to decrease enzymatic capacity; and poor metabolisers have no functionally active alleles and have minimal or no enzyme activity (Stamer et al, 2007; Stamer & Stuber, 2007). In Caucasian populations, 8% to 10% of people are poor metabolisers; however 3% to 5% are ultrarapid metabolisers (Stamer & Stuber, 2007).

For additional detail related to individual opioids see Section 4.1.2.

Codeine

In children and adults receiving codeine for postoperative pain, very low or undetectable levels of plasma morphine have been noted in those with poor metaboliser or intermediate metaboliser genotypes, but with variable impact on analgesia (Williams et al, 2002 **Level II**; Poulsen et al, 1998 **Level IV**; Persson et al, 1995 **Level IV**).

CYP2D6 genotypes predicting ultrarapid metabolism (CYP2D6 gene duplication) resulted in about 50% higher plasma concentrations of morphine and its glucuronides following oral codeine compared with the extensive metabolisers (Kirchheiner et al, 2007 **Level IV**). Both the impaired renal clearance of metabolites and genetic background (CYP2D6 ultrarapid metaboliser status) have been implicated in reports of respiratory depression due to codeine (Stamer & Stuber, 2007 **Level IV**). Morphine toxicity and death has been reported in a breastfed neonate whose mother was an ultrarapid metaboliser of codeine (Madadi et al, 2007). CYP2D6 genotyping predicts subjects with reduced metabolism to morphine, but must be combined with additional phenotyping to accurately predict patients at risk of morphine toxicity (Lotsch et al, 2009 **Level III-2**).

Tramadol

O-demethylation of tramadol by CYP2D6 produces the active metabolite (+)-O-desmethyltramadol or M1, which has an affinity for mu-opioid receptors that is approximately 200 times more than the parent drug (Shipton, 2000). Poor metabolisers have significantly lower plasma concentrations of M1 compared with both homozygous and heterozygous extensive metabolisers (Stamer et al, 2003 **Level III-3**; Fliegert et al, 2005 **Level II**) and experience less analgesia (Poulsen et al, 1998 **Level IV**; Stamer et al, 2003 **Level III-3**). The selective serotonin reuptake inhibitor (SSRI) paroxetine (a CYP2D6 inhibitor) significantly inhibited (+) and (-) tramadol metabolism by about a third (Laugesen et al, 2005 **Level II**). As with codeine, impaired renal clearance of metabolites and genetic background (CYP26 ultrarapid metaboliser status) have been implicated in cases of respiratory depression after tramadol (Desmeules et al, 1996 **Level II**).

Methadone

Genetic polymorphisms in genes coding for methadone-metabolising enzymes, transporter proteins (p-glycoprotein), and mu-opioid receptors may explain part of the observed inter-individual variation in the pharmacokinetics and pharmacodynamics of methadone; blood concentrations may vary up to 20-fold for a given dose (Li et al, 2008).

Cytochrome P450 (CYP) 2B6 and 3A4 have been identified as the main CYP isoforms involved in methadone metabolism, but CYP2D6 has also been reported to have an effect (Li et al, 2008). Differing effects for isomers of methadone have also been reported. Genetic variability in CYP2B6 influenced (S)-, and to a lesser extent, plasma (R)-methadone concentrations; fluoxetine (CYP2D6 inhibitor) only increased (R)-methadone (Kharasch et al, 2004 **Level III-1**); and paroxetine (CYP2D6 inhibitor) increased steady-state (R)-, (S)-, and (R, S)-methadone in extensive metabolisers, but only increased (S)-methadone in poor metaboliser genotypes (Anderson & Palmer, 2006).

NSAIDs

Wide variability in gene expression and functional polymorphisms in the COX-2 gene (PTGS2) may explain part of the inter-individual variations in acute pain and the analgesic efficacy of non-selective NSAIDs (nsNSAIDs) and coxibs; this may be useful to predict patient risk and benefit to drugs based on individual genetic variations (Somogyi et al, 2007; Lee et al, 2006 **Level III-2**).

NsNSAIDs like ibuprofen, naproxen and piroxicam are metabolised by CYP2C9 (Rollason et al, 2008). Between 1% and 3% of Caucasians are poor metabolisers. Homozygous carriers of the CYP2D9* 3 allele may accumulate celecoxib and ibuprofen in blood and tissues and be at risk of increased adverse effects (Kirchheiner et al, 2003 **Level III-3**; Kirchheiner et al, 2002 **Level IV**; Stamer & Stuber, 2007).

Key messages

1. CYP2D6 polymorphisms affect plasma concentrations of active metabolites of codeine and tramadol (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion.

- Genetic polymorphisms explain the wide inter-individual variability in plasma concentrations of a given dose of methadone (**N**).

REFERENCES

- Aasvang EK & Kehlet H (2007) Chronic pain after childhood groin hernia repair. *J Pediatr Surg* **42**(8): 1403–8.
- Aasvang EK, Brandsborg B, Christensen B et al (2008) Neurophysiological characterization of postherniotomy pain. *Pain* **137**(1): 173–81.
- Ahlers O, Nachtigall I, Lenze J et al (2008) Intraoperative thoracic epidural anaesthesia attenuates stress-induced immunosuppression in patients undergoing major abdominal surgery. *Br J Anaesth* **101**(6): 781–7.
- Andersen LO, Gaarn-Larsen L, Kristensen BB et al (2009) Subacute pain and function after fast-track hip and knee arthroplasty. *Anaesthesia* **64**(5): 508–13.
- Anderson BJ & Palmer GM (2006) Recent pharmacological advances in paediatric analgesics. *Biomed Pharmacother* **60**(7): 303–9.
- Ballantyne JC, Carr DB, deFerranti S et al (1998) The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. *Anesth Analg* **86**(3): 598–612.
- Basse L, Raskov HH, Hjort Jakobsen D et al (2002) Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. *Br J Surg* **89**(4): 446–53.
- Batoz H, Verdonck O, Pellerin C et al (2009) The analgesic properties of scalp infiltrations with ropivacaine after intracranial tumoral resection. *Anesth Analg* **109**(1): 240–4.
- Beattie WS, Badner NH & Choi P (2001) Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. *Anesth Analg* **93**(4): 853–8.
- Biki B, Mascha E, Moriarty DC et al (2008) Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology* **109**(2): 180–7.
- Birbaumer N, Flor H & Lutzenberger W (1995) The corticalization of chronic pain. In: *Pain and the Brain: From Nociception to Cognition. Advances in Pain Research and Therapy* edn. Burkhart B and Desmedt JE (eds). New York, Raven Press.
- Bisgaard T, Klarskov B, Rosenberg J et al (2001) Characteristics and prediction of early pain after laparoscopic cholecystectomy. *Pain* **90**(3): 261–9.
- Blumenthal S, Dullenkopf A, Rentsch K et al (2005) Continuous infusion of ropivacaine for pain relief after iliac crest bone grafting for shoulder surgery. *Anesthesiology* **102**(2): 392–7.
- Blyth FM, March LM & Cousins MJ (2003) Chronic pain-related disability and use of analgesia and health services in a Sydney community. *Med J Aust* **179**(2): 84–7.
- Bong CL, Samuel M, Ng JM et al (2005) Effects of preemptive epidural analgesia on post-thoracotomy pain. *J Cardiothorac Vasc Anesth* **19**(6): 786–93.
- Brander V, Gondek S, Martin E et al (2007) Pain and depression influence outcome 5 years after knee replacement surgery. *Clin Orthop Relat Res* **464**: 21–6.
- Brander VA, Stulberg SD, Adams AD et al (2003) Predicting total knee replacement pain: a prospective, observational study. *Clin Orthop Relat Res* **416**: 27–36.
- Brandner B, Bromley L & Blagrove M (2002) Influence of psychological factors in the use of patient controlled analgesia. *Acute Pain* **4**: 53–56.
- Brandsborg B, Nikolajsen L, Hansen CT et al (2007) Risk factors for chronic pain after hysterectomy: a nationwide questionnaire and database study. *Anesthesiology* **106**(5): 1003–12.
- Carli F, Mayo N, Klubien K et al (2002) Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. *Anesthesiology* **97**(3): 540–9.
- Carli F & Schricker T (2009) Modification of Metabolic Response to Surgery by Neural Blockade. In: *Neural Blockade in Clinical Anesthesia and Pain Medicine* 4th edn. Cousins MJ, Bridenbaugh PO, Carr D and Horlocker T (eds). Philadelphia, Lippincott, Wolters Kluwer, Lippincott Williams & Wilkins.

- Carlson JD, Maire JJ, Martenson ME et al (2007) Sensitization of pain-modulating neurons in the rostral ventromedial medulla after peripheral nerve injury. *J Neurosci* **27**(48): 13222–31.
- Carr E, Brockbank K, Allen S et al (2006) Patterns and frequency of anxiety in women undergoing gynaecological surgery. *J Clin Nurs* **15**(3): 341–52.
- Caumo W, Schmidt AP, Schneider CN et al (2001) Risk factors for postoperative anxiety in adults. *Anaesthesia* **56**(8): 720–8.
- Caumo W, Schmidt AP, Schneider CN et al (2002) Preoperative predictors of moderate to intense acute postoperative pain in patients undergoing abdominal surgery. *Acta Anaesthesiol Scand* **46**(10): 1265–71.
- Caza N, Taha R, Qi Y et al (2008) The effects of surgery and anesthesia on memory and cognition. *Prog Brain Res* **169**: 409–22.
- Chandra RK (1983) Nutrition, immunity, and infection: present knowledge and future directions. *Lancet* **1**(8326 Pt 1): 688–91.
- Chapman CR, Tuckett RP & Song CW (2008) Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. *J Pain* **9**(2): 122–45.
- Choi PT, Bhandari M, Scott J et al (2003) Epidural analgesia for pain relief following hip or knee replacement. *Cochrane Database Syst Rev*(3): CD003071.
- Christensen T, Bendix T & Kehlet H (1982) Fatigue and cardiorespiratory function following abdominal surgery. *Br J Surg* **69**(7): 417–9.
- Christensen T, Nygaard E, Stage JG et al (1990) Skeletal muscle enzyme activities and metabolic substrates during exercise in patients with postoperative fatigue. *Br J Surg* **77**(3): 312–5.
- Cohen L, Fouladi RT & Katz J (2005) Preoperative coping strategies and distress predict postoperative pain and morphine consumption in women undergoing abdominal gynecologic surgery. *J Psychosom Res* **58**(2): 201–9.
- Cousins MJ, Power I & Smith G (2000) 1996 Labat lecture: pain—a persistent problem. *Reg Anesth Pain Med* **25**(1): 6–21.
- Cousins MJ, Brennan F & Carr DB (2004) Pain relief: a universal human right. *Pain* **112**(1-2): 1–4.
- Craig KD (2006) The construct and definition of pain in developmental disability. In: *Pain in individuals with developmental disabilities*. Symons FJ and Oberlander, TF (eds). Brookes, Baltimore.
- Craig KD (2009) The social communication model of pain. *Canadian Psychology* **50**(1): 22–32.
- Crombez G, Eccleston C (2002) To express or suppress may be a function of others' distress. *Behavioral and Brain Sciences* **25**: 457.
- Cummins TR, Sheets PL & Waxman SG (2007) The roles of sodium channels in nociception: Implications for mechanisms of pain. *Pain* **131**(3): 243–57.
- Dahl JB & Moiniche S (2004) Pre-emptive analgesia. *Br Med Bull* **71**: 13–27.
- de Andrade DC, Baudic S, Attal N et al (2008) Beyond neuropathy in hereditary sensory and autonomic neuropathy type V: cognitive evaluation. *Eur J Neurol* **15**(7): 712–9.
- De Cosmo G, Congedo E, Lai C et al (2008) Preoperative psychologic and demographic predictors of pain perception and tramadol consumption using intravenous patient-controlled analgesia. *Clin J Pain* **24**(5): 399–405.
- Delaney CP, Zutshi M, Senagore AJ et al (2003) Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum* **46**(7): 851–9.
- Desmeules JA, Piguët V, Collart L et al (1996) Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br J Clin Pharmacol* **41**(1): 7–12.
- Diatchenko L, Slade GD, Nackley AG et al (2005) Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* **14**(1): 135–43.
- Dib-Hajj SD, Yang Y & Waxman SG (2008) Genetics and molecular pathophysiology of Na(v)1.7-related pain syndromes. *Adv Genet* **63**: 85–110.

Dib-Hajj SD, Binshtok AM, Cummins TR et al (2009) Voltage-gated sodium channels in pain states: Role in pathophysiology and targets for treatment. *Brain Res Rev* **60**(1): 65–83.

Donatelli F, Schricker T, Mistraletti G et al (2006) Postoperative infusion of amino acids induces a positive protein balance independently of the type of analgesia used. *Anesthesiology* **105**(2): 253–9.

Drenth JP & Waxman SG (2007) Mutations in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. *J Clin Invest* **117**(12): 3603–9.

Duale C, Sibaud F, Guastella V et al (2009) Perioperative ketamine does not prevent chronic pain after thoracotomy. *Eur J Pain* **13**(5): 497–505.

Eccleston C (2001) Role of psychology in pain management. *Br J Anaesth* **87**(1): 144–52.

Eccleston C & Crombez G (1999) Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull* **125**(3): 356–66.

Engel GL (1977) The need for a new medical model: a challenge for biomedical science. *Science* **196**: 129–36.

Exadaktylos AK, Buggy DJ, Moriarty DC et al (2006) Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* **105**(4): 660–4.

Fahy BG, Sheehy AM & Coursin DB (2009) Glucose control in the intensive care unit. *Crit Care Med* **37**(5): 1769–76.

Fassoulaki A, Sarantopoulos C, Melemini A et al (2000) EMLA reduces acute and chronic pain after breast surgery for cancer. *Reg Anesth Pain Med* **25**(4): 350–5.

Fassoulaki A, Patris K, Sarantopoulos C et al (2002) The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesth Analg* **95**(4): 985–91.

Fassoulaki A, Triga A, Melemini A et al (2005) Multimodal analgesia with gabapentin and local anesthetics prevents acute and chronic pain after breast surgery for cancer. *Anesth Analg* **101**(5): 1427–32.

Fillingim RB, Kaplan L, Staud R et al (2005) The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. *J Pain* **6**(3): 159–67.

Flacker JM & Lipsitz LA (1999) Neural mechanisms of delirium: current hypotheses and evolving concepts. *J Gerontol A Biol Sci Med Sci* **54**(6): B239–46.

Fliegert F, Kurth B & Gohler K (2005) The effects of tramadol on static and dynamic pupillometry in healthy subjects—the relationship between pharmacodynamics, pharmacokinetics and CYP2D6 metaboliser status. *Eur J Clin Pharmacol* **61**(4): 257–66.

Flor H, Elbert T, Knecht S et al (1995) Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* **375**(6531): 482–4.

Flor H, Knost B & Birbaumer N (2002) The role of operant conditioning in chronic pain: an experimental investigation. *Pain* **95**(1–2): 111–8.

Flor H & Hermann C (2004) Biopsychosocial models of pain. In: *Psychosocial Aspects of Pain: a Handbook for Health Care Providers. Progress in Pain Research and Management* edn. Dworkin RH and Breitbart WS (eds). Seattle, IASP Press.

Forsythe ME, Dunbar MJ, Hennigar AW et al (2008) Prospective relation between catastrophizing and residual pain following knee arthroplasty: two-year follow-up. *Pain Res Manag* **13**(4): 335–41.

Gao L, Taha R, Gauvin D et al (2005) Postoperative cognitive dysfunction after cardiac surgery. *Chest* **128**(5): 3664–70.

Gear RW, Gordon NC, Heller PH et al (1996) Gender difference in analgesic response to the kappa-opioid pentazocine. *Neurosci Lett* **205**(3): 207–9.

Gear RW, Miaskowski C, Gordon NC et al (1999) The kappa opioid nalbuphine produces gender- and dose-dependent analgesia and antianalgesia in patients with postoperative pain. *Pain* **83**(2): 339–45.

Gil KM, Ginsberg B, Muir M et al (1990) Patient-controlled analgesia in postoperative pain: the relation of psychological factors to pain and analgesic use. *Clin J Pain* **6**(2): 137–42.

Gil KM, Ginsberg B, Muir M et al (1992) Patient controlled analgesia: the relation of psychological factors to pain and analgesic use in adolescents with postoperative pain. *Clin J Pain* **8**(3): 215–21.

- Granot M & Ferber SG (2005) The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. *Clin J Pain* **21**(5): 439–45.
- Gray P (2008) Acute neuropathic pain: diagnosis and treatment. *Curr Opin Anaesthesiol* **21**(5): 590–5.
- Greisen J, Juhl CB, Grofte T et al (2001) Acute pain induces insulin resistance in humans. *Anesthesiology* **95**(3): 578–84.
- Grusser SM, Muhlnickel W, Schaefer M et al (2004) Remote activation of referred phantom sensation and cortical reorganization in human upper extremity amputees. *Exp Brain Res* **154**(1): 97–102.
- Hansen N, Klein T, Magerl W et al (2007) Psychophysical evidence for long-term potentiation of C-fiber and A-delta fiber pathways in humans by analysis of pain descriptors. *J Neurophysiol* **97**(3): 2559–63.
- Harrison RA, Lewin MR, Halliday D et al (1989) Leucine kinetics in surgical patients. I: A study of the effect of surgical 'stress'. *Br J Surg* **76**(5): 505–8.
- Hayes C, Browne S, Lantry G et al (2002) Neuropathic pain in the acute pain service: a prospective study. *Acute Pain* **4**: 45–48.
- Heinricher MM, Tavares I, Leith JL et al (2009) Descending control of nociception: Specificity, recruitment and plasticity. *Brain Res Rev* **60**(1): 214–25.
- Herroeder S, Pecher S, Schönherr ME et al (2007) Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Ann Surg* **246**(2): 192–200.
- Hines S, Theodorou S, Williamson A et al (2008) Management of acute pain in methadone maintenance therapy in-patients. *Drug Alcohol Rev* **27**(5): 519–23.
- Hinrichs-Rocker A, Schulze K, Järvinen I et al (2009) Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) – A systematic review. *Eur J Pain* **13**: 719–30
- Hjortso NC, Neumann P, Frosig F et al (1985) A controlled study on the effect of epidural analgesia with local anaesthetics and morphine on morbidity after abdominal surgery. *Acta Anaesthesiol Scand* **29**(8): 790–6.
- Hobson JA, Slade P, Wrench IJ et al (2006) Preoperative anxiety and postoperative satisfaction in women undergoing elective caesarean section. *Int J Obstet Anesth* **15**(1): 18–23.
- Hsu YW, Somma J, Hung YC et al (2005) Predicting postoperative pain by preoperative pressure pain assessment. *Anesthesiology* **103**(3): 613–8.
- Hunt SP & Mantyh PW (2001) The molecular dynamics of pain control. *Nat Rev Neurosci* **2**(2): 83–91.
- Jacobsen PB & Butler RW (1996) Relation of cognitive coping and catastrophizing to acute pain and analgesic use following breast cancer surgery. *J Behav Med* **19**(1): 17–29.
- Jakobsen DH, Sonne E, Andreassen J et al (2006) Convalescence after colonic surgery with fast-track vs conventional care. *Colorectal Dis* **8**(8): 683–7.
- Jamison RN, Taft K, O'Hara JP et al (1993) Psychosocial and pharmacologic predictors of satisfaction with intravenous patient-controlled analgesia. *Anesth Analg* **77**(1): 121–5.
- Ji RR, Gereau RWt, Malcangio M et al (2009) MAP kinase and pain. *Brain Res Rev* **60**(1): 135–48.
- Jolliffe CD & Nicholas MK (2004) Verbally reinforcing pain reports: an experimental test of the operant model of chronic pain. *Pain* **107**(1-2): 167–75.
- Jorgensen H, Wetterslev J, Moiniche S et al (2000) Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev*(4): CD001893.
- Joshi GP (2005) Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. *Anesth Analg* **101**(2): 601–5.
- Kairaluoma PM, Bachmann MS, Rosenberg PH et al (2006) Preincisional paravertebral block reduces the prevalence of chronic pain after breast surgery. *Anesth Analg* **103**(3): 703–8.
- Kalkman CJ, Visser K, Moen J et al (2003) Preoperative prediction of severe postoperative pain. *Pain* **105**(3): 415–23.
- Katz J & McCartney CJ (2002) Current status of preemptive analgesia. *Curr Opin Anaesthesiol* **15**(4): 435–41.

- Katz J, Poleshuck EL, Andrus CH et al (2005) Risk factors for acute pain and its persistence following breast cancer surgery. *Pain* **119**(1-3): 16–25.
- Katz J & Clarke H (2008) Preventive analgesia and beyond: current status, evidence, and future directions. In: *Clinical Pain Management: Acute Pain* 2nd edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.
- Katz J, Buis T & Cohen L (2008) Locked out and still knocking: predictors of excessive demands for postoperative intravenous patient-controlled analgesia. *Can J Anaesth* **55**(2): 88–99.
- Kehlet H & Dahl JB (2003) Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* **362**(9399): 1921–8.
- Kehlet H, Jensen TS & Woolf CJ (2006) Persistent postsurgical pain: risk factors and prevention. *Lancet* **367**(9522): 1618–25.
- Kehlet H, Wilkinson RC, Fischer HB et al (2007) PROSPECT: evidence-based, procedure-specific postoperative pain management. *Best Pract Res Clin Anaesthesiol* **21**(1): 149–59.
- Kehlet H & Wilmore DW (2008) Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* **248**(2): 189–98.
- Keogh E & Cochrane M (2002) Anxiety sensitivity, cognitive biases, and the experience of pain. *J Pain* **3**(4): 320–9.
- Kharasch ED, Hoffer C, Whittington D et al (2004) Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. *Clin Pharmacol Ther* **76**(3): 250–69.
- Khoo CK, Vickery CJ, Forsyth N et al (2007) A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. *Ann Surg* **245**(6): 867–72.
- Kim H, Clark D & Dionne RA (2009) Genetic contributions to clinical pain and analgesia: avoiding pitfalls in genetic research. *J Pain* **10**(7): 663–93.
- Kirchheiner J, Meineke I, Freytag G et al (2002) Enantiospecific effects of cytochrome P450 2C9 amino acid variants on ibuprofen pharmacokinetics and on the inhibition of cyclooxygenases 1 and 2. *Clin Pharmacol Ther* **72**(1): 62–75.
- Kirchheiner J, Stormer E, Meisel C et al (2003) Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. *Pharmacogenetics* **13**(8): 473–80.
- Kirchheiner J, Schmidt H, Tzvetkov M et al (2007) Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J* **7**(4): 257–65.
- Kissin I (1994) Preemptive analgesia: terminology and clinical relevance. *Anesth Analg* **79**(4): 809–10.
- Klepstad P, Ravvag TT, Kaasa S et al (2004) The 118 A > G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. *Acta Anaesthesiol Scand* **48**(10): 1232–9.
- Korvald C, Elvenes OP & Myrmet T (2000) Myocardial substrate metabolism influences left ventricular energetics in vivo. *Am J Physiol Heart Circ Physiol* **278**(4): H1345–51.
- Kudoh A, Katagai H & Takazawa T (2002) Increased postoperative pain scores in chronic depression patients who take antidepressants. *J Clin Anesth* **14**(6): 421–5.
- Kunz M, Mylius V, Schepelmann K, Lautenbacher S (2004) On the relationship between self-report and facial expression of pain. *Journal of Pain* **5**: 367–376.
- Kuo CP, Jao SW, Chen KM et al (2006) Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth*. **97**(5): 640–6.
- Landau R, Kern C, Columb MO et al (2008) Genetic variability of the mu-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women. *Pain* **139**(1): 5–14.
- Laugesen S, Enggaard TP, Pedersen RS et al (2005) Paroxetine, a cytochrome P450 2D6 inhibitor, diminishes the stereoselective O-demethylation and reduces the hypoalgesic effect of tramadol. *Clin Pharmacol Ther* **77**(4): 312–23.

- Lavand'homme P, De Kock M & Waterloos H (2005) Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. *Anesthesiology* **103**(4): 813–20.
- Lazar HL, Chipkin SR, Fitzgerald CA et al (2004) Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. *Circulation* **109**(12): 1497–502.
- Lee YS, Kim H, Wu TX et al (2006) Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. *Clin Pharmacol Ther* **79**(5): 407–18.
- Leeuw M, Goossens ME, Linton SJ et al (2007) The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med* **30**(1): 77–94.
- Li Y, Kantelip JP, Gerritsen-van Schieveen P et al (2008) Interindividual variability of methadone response: impact of genetic polymorphism. *Mol Diagn Ther* **12**(2): 109–24.
- Lingard EA & Riddle DL (2007) Impact of psychological distress on pain and function following knee arthroplasty. *J Bone Joint Surg Am* **89**(6): 1161–9.
- Linton SJ (2000) A review of psychological risk factors in back and neck pain. *Spine* **25**(9): 1148–56.
- Liu Q, Docherty JC, Rendell JC et al (2002) High levels of fatty acids delay the recovery of intracellular pH and cardiac efficiency in post-ischemic hearts by inhibiting glucose oxidation. *J Am Coll Cardiol* **39**(4): 718–25.
- Liu SS, Block BM & Wu CL (2004) Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. *Anesthesiology* **101**(1): 153–61.
- Liu SS & Wu CL (2008) Neural blockade: impact on outcome. In: *Neural Blockade in Clinical Anesthesia and Pain Medicine* 4th edn. Cousins MJ, Bridenbaugh PO, Carr D and Horlocker T (eds). Philadelphia, Wolters Kluwer, Lippincott, Williams & Wilkins.
- Loeser JD & Treede RD (2008) The Kyoto protocol of IASP Basic Pain Terminology. *Pain* **137**(3): 473–7.
- Lotsch J & Geisslinger G (2006) Current evidence for a genetic modulation of the response to analgesics. *Pain* **121**(1-2): 1–5.
- Lotsch J, Rohrbacher M, Schmidt H et al (2009) Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? *Pain* **144**(1-2): 119–24.
- Lotsch J, Stuck B & Hummel T (2006) The human mu-opioid receptor gene polymorphism 118A > G decreases cortical activation in response to specific nociceptive stimulation. *Behav Neurosci* **120**(6): 1218–24.
- Lugli AK, Donatelli F, Schricker T et al (2008) Epidural analgesia enhances the postoperative anabolic effect of amino acids in diabetes mellitus type 2 patients undergoing colon surgery. *Anesthesiology* **108**(6): 1093–9.
- Macrae WA (2008) Chronic post-surgical pain: 10 years on. *Br J Anaesth* **101**(1): 77–86.
- Madadi P, Koren G, Cairns J et al (2007) Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. *Can Fam Physician* **53**(1): 33–5.
- Malekpour F, Mirhashemi SH, Hajinasrolah E et al (2008) Ilioinguinal nerve excision in open mesh repair of inguinal hernia—results of a randomized clinical trial: simple solution for a difficult problem? *Am J Surg* **195**(6): 735–40.
- McCartney CJ, Sinha A & Katz J (2004) A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. *Anesth Analg* **98**(5): 1385–400.
- Merskey H & Bogduk N (1994) *Classification of Chronic Pain, IASP Task Force on Taxonomy*. Seattle, IASP Press.
- Mikus G & Weiss J (2005) Influence of CYP2D6 genetics on opioid kinetics, metabolism and response. *Curr Pharmacogenom* **3**: 43–52.
- Millan MJ (2002) Descending control of pain. *Prog Neurobiol* **66**(6): 355–474.
- Mogil JS (1999) The genetic mediation of individual differences in sensitivity to pain and its inhibition. *Proc Natl Acad Sci U S A* **96**(14): 7744–51.

- Mogil JS, Wilson SG, Chesler EJ et al (2003) The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. *Proc Natl Acad Sci U S A* **100**(8): 4867–72.
- Mogil JS, Ritchie J, Smith SB et al (2005) Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. *J Med Genet* **42**(7): 583–7.
- Moiniche S, Kehlet H & Dahl JB (2002) A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. *Anesthesiology* **96**(3): 725–41.
- Momin A & Wood JN (2008) Sensory neuron voltage-gated sodium channels as analgesic drug targets. *Curr Opin Neurobiol* **18**(4): 383–8.
- Monk TG, Weldon BC, Garvan CW et al (2008) Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* **108**(1): 18–30.
- Montagna P (2007) Recent advances in the pharmacogenomics of pain and headache. *Neurol Sci* **28** (Suppl 2): S208–12.
- Nackley AG, Tan KS, Fecho K et al (2007) Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta2- and beta3-adrenergic receptors. *Pain* **128**(3): 199–208.
- Nelson FV, Zimmerman L, Barnason S et al (1998) The relationship and influence of anxiety on postoperative pain in the coronary artery bypass graft patient. *J Pain Symptom Manage* **15**(2): 102–9.
- Newman S, Stygall J, Hirani S et al (2007) Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. *Anesthesiology* **106**(3): 572–90.
- Nikolajsen L, Sorensen HC, Jensen TS et al (2004) Chronic pain following Caesarean section. *Acta Anaesthesiol Scand* **48**(1): 111–6.
- Nishimori M, Ballantyne JC & Low JH (2006) Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. *Cochrane Database Syst Rev* **3**: CD005059.
- Oertel B & Lotsch J (2008) Genetic mutations that prevent pain: implications for future pain medication. *Pharmacogenomics* **9**(2): 179–94.
- Oliver MF & Opie LH (1994) Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. *Lancet* **343**(8890): 155–8.
- Ong CK, Lirk P, Seymour RA et al (2005) The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg* **100**(3): 757–73.
- Ozalp G, Sarioglu R, Tuncel G et al (2003) Preoperative emotional states in patients with breast cancer and postoperative pain. *Acta Anaesthesiol Scand* **47**(1): 26–9.
- Park JJ, Lee J, Kim MA et al (2007) Induction of total insensitivity to capsaicin and hypersensitivity to garlic extract in human by decreased expression of TRPV1. *Neurosci Lett* **411**(2): 87–91.
- Parker MJ, Handoll HH & Griffiths R (2004) Anaesthesia for hip fracture surgery in adults. *Cochrane Database Syst Rev*(4): CD000521.
- Patapoutian A, Tate S & Woolf CJ (2009) Transient receptor potential channels: targeting pain at the source. *Nat Rev Drug Discov* **8**(1): 55–68.
- Pavlin DJ, Sullivan MJ, Freund PR et al (2005) Catastrophizing: a risk factor for postsurgical pain. *Clin J Pain* **21**(1): 83–90.
- Perry F, Parker RK, White PF et al (1994) Role of psychological factors in postoperative pain control and recovery with patient-controlled analgesia. *Clinical Journal of Pain* **10**(1): 57–63.
- Persson K, Sjostrom S, Sigurdardottir I et al (1995) Patient-controlled analgesia (PCA) with codeine for postoperative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan. *Br J Clin Pharmacol* **39**(2): 182–6.
- Picchio M, Palimento D, Attanasio U et al (2004) Randomized controlled trial of preservation or elective division of ilioinguinal nerve on open inguinal hernia repair with polypropylene mesh. *Arch Surg* **139**(7): 755–8.
- Pincus T, Vlaeyen JW, Kendall NA et al (2002) Cognitive-behavioral therapy and psychosocial factors in low back pain: directions for the future. *Spine* **27**(5): E133–8.
- Pogatzki-Zahn EM & Zahn PK (2006) From preemptive to preventive analgesia. *Curr Opin Anaesthesiol* **19**(5): 551–5.

- Poulsen L, Riishede L, Brosen K et al (1998) Codeine in post-operative pain. Study of the influence of sparteine phenotype and serum concentrations of morphine and morphine-6-glucuronide. *Eur J Clin Pharmacol* **54**(6): 451–4.
- Quintner JL, Cohen ML, Buchanan D, Katz JD, Williamson OD (2008). Pain medicine and its models: helping or hindering? *Pain Med* **9**:824–34.
- Ready LB & Edwards WT (1992) *Management of Acute Pain: a Practical Guide. Taskforce on Acute Pain*. Seattle, IASP Publications.
- Reyes-Gibby CC, Shete S, Ravvag T et al (2007) Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene. *Pain* **130**(1-2): 25–30.
- Rigg JR, Jamrozik K, Myles PS et al (2002) Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* **359**(9314): 1276–82.
- Rodgers A, Walker N, Schug S et al (2000) Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ* **321**(7275): 1493.
- Rollason V, Samer C, Piguet V et al (2008) Pharmacogenetics of analgesics: toward the individualization of prescription. *Pharmacogenomics* **9**(7): 905–33.
- Roth ML, Tripp DA, Harrison MH et al (2007) Demographic and psychosocial predictors of acute perioperative pain for total knee arthroplasty. *Pain Res Manag* **12**(3): 185–94.
- Rudin A, Wolner-Hanssen P, Hellbom M et al (2008) Prediction of post-operative pain after a laparoscopic tubal ligation procedure. *Acta Anaesthesiol Scand* **52**(7): 938–45.
- Russell FA & McDougall JJ (2009) Proteinase activated receptor (PAR) involvement in mediating arthritis pain and inflammation. *Inflamm Res* **58**(3): 119–26.
- Sandkuhler J (2009) Models and mechanisms of hyperalgesia and allodynia. *Physiol Rev* **89**(2): 707–58.
- Schafers M & Sorkin L (2008) Effect of cytokines on neuronal excitability. *Neurosci Lett* **437**(3): 188–93.
- Schott GD (1986) Pain and its absence in an unfortunate family of amputees. *Pain* **25**(2): 229–31.
- Schricker T, Meterissian S, Lattermann R et al (2008) Anticatabolic effects of avoiding preoperative fasting by intravenous hypocaloric nutrition: a randomized clinical trial. *Ann Surg* **248**(6): 1051–9.
- Searle R & Hopkins PM (2009) Pharmacogenomic variability and anaesthesia. *Br J Anaesth* **103**(1): 14–25.
- Senturk M, Ozcan PE, Talu GK et al (2002) The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* **94**(1): 11–5.
- Shipton EA (2000) Tramadol—present and future. *Anaesth Intensive Care* **28**(4): 363–74.
- Sloane EM, Soderquist RG, Maier SF et al (2009) Long-term control of neuropathic pain in a non-viral gene therapy paradigm. *Gene Ther* **16**(4): 470–5.
- Somogyi AA, Barratt DT & Collier JK (2007) Pharmacogenetics of opioids. *Clin Pharmacol Ther* **81**(3): 429–44.
- Stamer UM, Lehnen K, Hothker F et al (2003) Impact of CYP2D6 genotype on postoperative tramadol analgesia. *Pain* **105**(1-2): 231–8.
- Stamer UM & Stuber F (2007) Genetic factors in pain and its treatment. *Curr Opin Anaesthesiol* **20**(5): 478–84.
- Stamer UM, Musshoff F, Kobilay M et al (2007) Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clin Pharmacol Ther* **82**(1): 41–7.
- Stein C, Clark JD, Oh U et al (2009) Peripheral mechanisms of pain and analgesia. *Brain Res Rev* **60**(1): 90–113.
- Strulov L, Zimmer EZ, Granot M et al (2007) Pain catastrophizing, response to experimental heat stimuli, and post-cesarean section pain. *J Pain* **8**(3): 273–9.
- Sullivan M, Tanzer M, Stanish W et al (2009) Psychological determinants of problematic outcomes following Total Knee Arthroplasty. *Pain* **143**(1-2): 123–9.
- Suzuki R, Rygh LJ & Dickenson AH (2004) Bad news from the brain: descending 5-HT pathways that control spinal pain processing. *Trends Pharmacol Sci* **25**(12): 613–7.

- Suzuki M, Haraguti S, Sugimoto K et al (2006) Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology* **105**(1): 111–9.
- Tegeder I, Costigan M, Griffin RS et al (2006) GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nat Med* **12**(11): 1269–77.
- Tegeder I, Adolph J, Schmidt H et al (2008) Reduced hyperalgesia in homozygous carriers of a GTP cyclohydrolase 1 haplotype. *Eur J Pain* **12**(8): 1069–77.
- Terry R, Niven C, Brodie E et al (2007) An exploration of the relationship between anxiety, expectations and memory for postoperative pain. *Acute Pain* **9**: 135–43.
- Tetrault JM & O'Connor PG (2008) Substance abuse and withdrawal in the critical care setting. *Crit Care Clin* **24**(4): 767–88.
- Thomas V, Heath M, Rose D et al (1995) Psychological characteristics and the effectiveness of patient-controlled analgesia. *Br J Anaesth* **74**(3): 271–6.
- Tracey I & Mantyh PW (2007) The cerebral signature for pain perception and its modulation. *Neuron* **55**(3): 377–91.
- Tracey I (2008) Imaging pain. *Br J Anaesth* **101**(1): 32–9.
- Turk DC & Monarch ES (1995) Biopsychosocial perspective on chronic pain. In: *Psychological Approaches to Pain Management* 2nd edn. Turk DC and Gatchel RJ (eds). New York, Guildford Press.
- Van den Berghe G (2004) How does blood glucose control with insulin save lives in intensive care? *J Clin Invest* **114**(9): 1187–95.
- Vancleef LM & Peters ML (2006) Pain catastrophizing, but not injury/illness sensitivity or anxiety sensitivity, enhances attentional interference by pain. *J Pain* **7**(1): 23–30.
- Vanegas H & Schaible HG (2004) Descending control of persistent pain: inhibitory or facilitatory? *Brain Res Brain Res Rev* **46**(3): 295–309.
- Vervoot T, Goubert L, Crombez G (2009) The relationship between high catastrophizing children's facial display of pain and parental judgment of their child's pain. *Pain* **142**: 142–148.
- Wall PD (1988) The prevention of postoperative pain. *Pain* **33**(3): 289–90.
- Watters JM, Clancey SM, Moulton SB et al (1993) Impaired recovery of strength in older patients after major abdominal surgery. *Ann Surg* **218**(3): 380–90.
- White PF, Kehlet H, Liu S (2009) Perioperative analgesia: what do we still know? *Anesth Analg* **108**: 1364–7.
- White PF, Kehlet H, Neal JM et al; Fast-Track Surgery Study Group (2007). The role of the anesthesiologist in fast-track surgery: from multimodal analgesia to perioperative medical care. *Anesth Analg* **104**(6): 1380–96.
- White FA & Wilson NM (2008) Chemokines as pain mediators and modulators. *Curr Opin Anaesthesiol* **21**(5): 580–5.
- Wieczorek S, Bergstrom J, Saaf M et al (2008) Expanded HSAN4 phenotype associated with two novel mutations in NTRK1. *Neuromuscul Disord* **18**(8): 681–4.
- Wiener RS, Wiener DC & Larson RJ (2008) Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* **300**(8): 933–44.
- Williams DG, Patel A & Howard RF (2002) Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* **89**(6): 839–45.
- Wilmore DW & Kehlet H (2001) Management of patients in fast track surgery. *BMJ* **322**(7284): 473–6.
- Wind J, Polle SW, Fung Kon Jin PH et al (2006) Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg* **93**(7): 800–9.
- Windsor JA & Hill GL (1988) Weight loss with physiologic impairment. A basic indicator of surgical risk. *Ann Surg* **207**(3): 290–6.
- Woolf CJ (1983) Evidence for a central component of post-injury pain hypersensitivity. *Nature* **306**(5944): 686–8.
- Woolf CJ & Salter MW (2000) Neuronal plasticity: increasing the gain in pain. *Science* **288**(5472): 1765–9.

Woolf CJ & Ma Q (2007) Nociceptors—noxious stimulus detectors. *Neuron* **55**(3): 353–64.

Wrigley PJ, Press SR, Gustin SM et al (2009) Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. *Pain* **141**(1-2): 52–9.

Xu H, Tian W, Fu Y et al (2007) Functional effects of nonsynonymous polymorphisms in the human TRPV1 gene. *Am J Physiol Renal Physiol* **293**(6): F1865–76.

Yarnitsky D, Crispel Y, Eisenberg E et al (2008) Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain* **138**(1): 22–8.

Young Casey C, Greenberg MA, Nicassio PM et al (2008) Transition from acute to chronic pain and disability: a model including cognitive, affective, and trauma factors. *Pain* **134**(1-2): 69–79.