1

Physiology and psychology of acute pain

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1.1 | Applied physiology of acute pain

1.1.1 | Definition of acute pain

Pain is most commonly described as *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"*, (Merskey 1994 **GL**). It should be noted that *"pain is subjective and indicates that each individual learns the application of the word through experiences related to injury in early life, and characterizes the experience as unpleasant, and therefore emotional as well as sensory in nature"* (IASP 2019a **GL**). Chronic pain has gradually emerged as a distinct phenomenon in comparison with acute pain with the IASP currently defining it as *"pain that lasts or recurs for longer than 3 months"* (Treede 2019 **GL**). Although acute pain cannot be precisely distinguished from chronic pain using time-based definitions, for pragmatic purposes recommended definitions continue to be time-based (Kent 2019 **GL**):

> *"Acute pain is considered to last up to seven days, with the following qualifications:*
> 1. *Its duration reflects the mechanism and severity of the underlying inciting event.*
> 2. *Prolongations from seven to 30 days are common.*
> 3. *Prolongations beyond the duration of acute pain but not extending past 90 days post onset/-injury are common. This refers to the ill-defined but important period of "subacute" pain that warrants further specification and consideration in future taxonomic, research, and regulatory efforts.*
> 4. *Our understanding of pain mechanisms is currently insufficient to link these durations to specific physiologic mechanisms."*

This section focuses on the physiology and pathophysiology of pain resulting from nociceptive activity in the sensory nervous system, but also introduces the neurobiology of pain as a beneficial adaptive brain state that responds to and can be altered by psychological factors. A more complete description of the classes of psychological factors that affect the experience of pain is outlined in Section 1.2; for paediatric information se Section 10.1.

1.1.2 | Nociceptive pathways and pain perception

The ability of the somatosensory system to detect noxious and potentially tissue-damaging stimuli (ie nociception) is an important protective feature that involves multiple interacting peripheral and central mechanisms (Sommer 2018 **NR**). In addition to the sensory effects, the perception and experience of pain is multifactorial and will be influenced by genetic, psychological and environmental factors in every individual (Tracey 2019 **NR EH**; Porreca 2017 **NR**; Vardeh 2016 **NR**).

1.1.2.1 | Peripheral nociceptors

The detection of noxious stimuli by specialised peripheral sensory nerve endings (nociceptors) first requires the transduction of noxious stimuli into electrical activity and the conduction of these nociceptive signals in peripheral sensory nerves to the central nervous system (CNS) (Sommer 2018 **NR**; Dubin 2010 **NR**; Woolf 2007 **NR**). Nociceptive primary 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. Distinct classes of nociceptors are activated by noxious stimuli, which include intense pressure, extreme temperatures (>40 to 45°C or <15°C) and damaging chemicals.

The most prevalent subclass of nociceptor is the C-fibre polymodal type, which responds to mechanical, thermal and chemical stimuli, whereas other subclasses are specialised mechanical, heat or cold nociceptors (Woolf 2007 **NR**).

The physiological properties of nociceptors are determined by the differential expression of a repertoire of transduction molecules (Dubin 2010 **NR**). The particular expression of these transducers determines which modalities are detected by each set of nociceptors. For example, the transient receptor potential (TRP) channel type vanilloid 1 (TRPV1) transduces noxious temperatures from 39–51°C and generates electrical receptor potentials in a class of polymodal C fibres. All nociceptor axons have free terminal endings without anatomically specialised transducers such as the Meissner's corpuscles and Merkel cells used by skin mechanoreceptors. However, it is now known that molecular transducers used by mechanosensitive neurons, such as Piezo1 and Piezo2, are also widely expressed by non-neuronal cells in skin and other organs that can bidirectionally interact with somatosensory terminals including nociceptors (Oetjen 2018 **NR**; Moehring 2018 **NR**). Nociceptors in visceral tissue show differences to those in somatic tissue but are much less well studied. In the viscera, high threshold specific nociceptors are unusual and most mechanosensitive afferents code stimulation in a linear manner, which can reach the noxious range. There is a large proportion of silent nociceptors in viscera, which are unresponsive under basal conditions and respond to heat and chemical stimuli in the presence of inflammation (Grundy 2019 **NR**; Gebhart 2016 **NR**).

Nociceptors may also be classified by their relationship to trophic factors (Denk 2017 **NR**). Some C-fibre nociceptors are dependent on nerve growth factor (NGF) and express tyrosine kinase receptor (TrkA), which is a neurotrophin receptor. Most of these nociceptors also express substance P and calcitonin gene-related peptide (CGRP) and are classed as peptidergic. Another class of C fibres are not peptidergic but have glial cell line-derived neurotrophic factor (GDNF) family receptors (GFR 1, GFR 2; and their co-receptor Ret) and are thereby targets for GDNF or neurturin, respectively**.** Next generation sequencing and transcriptional profiling (by bulk sequencing or single-cell RNA-Seq) has been used for unbiased classification of primary sensory neurons, including nociceptors (Iadorola 2018 **NR**; Emery 2018 **NR**). A large proportion of differentially expressed genes that define classes encode membrane ion channels and receptors that function in nociceptor transduction and transmission (Waxman 2014 **NR**; Gold 2010 **NR**). However, the function of other transcripts identified by this unbiased approach have yet to be determined. This is advancing our understanding and resolving the conflicting alignment between classes previously defined by molecular, neurochemical, developmental and physiological criteria (Gatto 2019 **NR**; Emery 2018 **NR**).

Nociceptor plasticity

Sensitisation is a characteristic of nociceptors (Woolf 2007 **NR**). The phenotypes of the nociceptors change in response to nerve injury and inflammation and are not static. This dynamic neural plasticity lowers the transduction threshold of nociceptors and contributes to primary hyperalgesia, which is defined as abnormal intensity of pain relative to the stimulus (Gold 2010 **NR**; Sandkuhler 2009 **NR**).

Sensitisation is most often produced by chemical signals of tissue damage: such as during infection, inflammation or ischaemia; disruption of cells; degranulation of mast cells; secretions from inflammatory cells; or following induction of enzymes such as cyclooxygenase-2 (COX-2) (Baral 2019 **NR**; Sommer 2018 **NR**; Oetjen 2018 **NR**). A majority of chemical mediators act locally at nociceptor terminals by directly targeting ion channels or indirectly by activating intracellular signalling via calcium-permeable channels (Bourinet 2014 **NR**) or membrane receptors (see Table 1.1). NGF, immune mediators and other chemicals including proteinases, cytokines such as

tumour necrosis factor (TNF) alpha, interleukins, and chemokines such as chemokine (C-C motif) ligand 3 (CC L3) all have an impact on sensitisation of nociceptors (see Table 1.1).

TRPV1 is an example of a nociceptor transducer that contributes to sensitisation in nociceptor terminals. This is achieved when the thermal and chemical sensitivity of TRPV1 is lowered following direct or indirect modulation by local inflammatory mediators or by noxious environmental chemicals such as capsaicin (which causes the perception of heat and pain elicited by chillies) (Henrich 2015 **Level III-1 EH**). Neuropeptides (substance P and CGRP) released from the activated peripheral terminals via peripheral antidromic axonal responses cause neurogenic inflammation by promoting vasodilation and plasma extravasation. This promotes recruitment of serum factors and inflammatory cells at the site of injury (Sousa-Valente 2018 **NR**). Nonsteroidal anti-inflammatory drugs (NSAIDs) modulate peripheral pain by reducing prostaglandin E2 (PGE_2) synthesis from locally induced COX-2. Inflammation also induces changes in protein synthesis in the cell body of neurons in the dorsal root ganglia (DRG) and trigeminal ganglia, and alters the expression and transport of receptors, such as TRPV1 and opioid receptors, to the peripheral nerve terminal (Woolf 2007 **NR**). The latter underlies the peripheral action of opioid agonists in inflamed tissue and could allow nociceptor modulation by immune cells (Stein 2009 **NR**).

Table 1.1 | Examples of receptors and ligands that function in transduction or primary and secondary hyperalgesia of nociceptive primary afferent or spinal cord neurons

	Subtype	Ligand/Stimulus
Ionotropic receptor		
TRP	TRPV1	heat (≥43°C, unsensitised), capsaicin, H^+ (protons)
	TRPV2	heat (≥52°C)
	TRPV3, TRPV4	warm (32–39°C)
	TRPA1	environmental irritants (mustard oil, nicotine, formaldehyde, acrolein)
	TRPM8	cool (≤26°C)
acid sensing	ASIC1-4, TRAAK/TREK	H^+ (protons)
glutamate	NMDA, AMPA Kainate, GLurR1-5, NR1-2	glutamate
nicotinic	nACh (multiple subtypes)	acetylcholine
purine	P2X1-6	ATP
serotonin	5-HT$_3$	5-HT
Metabotropic receptor		
bradykinin	B$_I$, B$_2$	bradykinin
cannabinoid	CB$_1$, CB$_2$ (TRPs, non-canonical)	anandamide, cannabidiol

	Subtype	Ligand/Stimulus
chemokine	CXCR2,CXCR5, CX3CR1	CXCL1, CXCl13, CCL2 (MCP1), et al.
histamine	H_1	histamine
Interleukin	IL1R, IL-31A/OSMR, et al.	IL-1 alpha, IL-6, IL-31, et al.
LPS	Toll-like receptor 4	lipopolysaccharides
Mas-related GPCRs	MRGPRD, MRGPRA3, MRGPRX1	β-alanine, BAM8-22, other orphan ligands
metabotropic glutamate	$mGLuR_{1,2/3,5}$	glutamate
prostanoids	EP_{1-4} IP	PGE_2 (prostaglandins) PGI_2 (prostacyclin)
proteinase	PAR_{1-4} (TRPs non-canonical)	protease
serotonin	$5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_4$	5-HT (serotonin)
tachykinin	neurokinin-1 (NK_1)	substance P, neurokinin A
tyrosine kinase receptor	TrkA, p75 neurotrophin	NGF (nerve growth factor)
TNR receptor	TNFR1, TNFr2	TNF (tumour necrosis factor)
Pore forming toxins		
haemolysin	-haemolysin, - haemolysin AB	Secreted by gram-positive bacteria (eg *S. aureus*)

Sources: Baral 2019; Sommer 2018; Harding 2018; Oetjen 2018; Gold 2010.

Similarly, NGF increases with inflammation, binds to TrkA, which causes phosphorylation of the TRPV1 and facilitates the sodium channels, which both increase nociceptor activity. In addition, NGF-TrkA complex is transported to the DRG, where it impacts on phenotypic changes resulting in changes to receptors and channels (Denk 2017 **NR**). NGF regulates relative amounts of neuropeptides and the threshold of nociceptors. The number of receptors for NGF (TrkA) is also determined by the functions of the corresponding DRG cells. Visceral primary afferents have a higher proportion of cells containing TrkA compared to somatic primary afferent neurons.

Sodium, potassium, calcium and chloride ion channels also function in nociceptor transduction and transmission. Sodium channels are a prerequisite for conduction of neuronal action potentials to the CNS (Bennett 2019 **NR**). 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 and specific alterations in the expression of sodium channels (upregulation or downregulation) contribute to hyperexcitability that occurs in different pain states and may explain part of the mechanism of benefit of systemic local anaesthetics in acute and chronic pain (see Section 4.4.1) . The importance of sodium channels

in pain sensitivity is reflected by the impact of human mutations in the SCN9A gene encoding the $Na_v1.7$ channel (Dib-Hajj 2019 **NR**) (see Section 1.7.1). Loss of function results in insensitivity to pain, whereas gain of function mutations can produce erythromelalgia and other severe pain. These effects are not restricted to sodium channels; functional and expression changes in other classes of calcium, potassium and chloride channels also contribute to nociceptive transmission and processing by nociceptors (Bennett 2019 **NR**).

Medicines that are specific blockers of sodium channel subtypes or cause state-dependent reductions in sodium channel activity are becoming available for evaluation in human clinical trials (Dib-Hajj 2019 **NR**). New ion channel targets are also emerging that, as well as regulators of afferent fibre excitability, include a separate class of ion channels that regulate the transfer of the nociceptive signal (synaptic transmission) from primary afferent fibres to the second-order neurons in the spinal cord (Yekkirala 2017 **NR**).

1.1.2.2 | Nociceptive transmission in the spinal cord

The cell bodies of nociceptive afferents that innervate the trunk, limbs and viscera are found in the DRG, while those innervating the head, oral cavity and neck are in the trigeminal ganglia and project to the brainstem trigeminal nucleus (Dubin 2010 **NR**). The central terminals of C and A-delta fibres convey information to nociceptive-specific areas within laminae I and II of the superficial dorsal horn and to wide dynamic range neurons in lamina V, which encode both innocuous and noxious information (Koch 2018 **NR**; Todd 2010 **NR**). By contrast, large myelinated A-beta fibres transmit light touch or innocuous mechanical stimuli to the deeper laminae III and IV (Moehring 2018 **NR**).

Primary afferent terminals activate dorsal horn neurons by releasing two major classes of neurotransmitter; glutamate as the primary transmitter and neuropeptides such as substance P, CGRP, galanin and somatostatin as cotransmitters (Sandkuhler 2009 **NR**). Depolarisation of the primary afferent terminal results in glutamate release, which activates postsynaptic ionotropic α-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 (Prescott 2014 **NR**; Sandkuhler 2009 **NR**).

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 (non-NMDA) and metabotropic (mGluR) glutamate receptors, 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. This mechanism has been implicated in learning and memory in the hippocampus and pain sensitisation in the spinal cord (Sandkuhler 2009 **NR**). Behavioural correlates of these electrophysiological phenomena have been seen in human volunteers as repeated stimuli elicit progressive increases in reported pain (Treede 2016 **NR**).

Intense and ongoing stimuli further increase the excitability of dorsal horn neurons, leading to central sensitisation (Woolf 2014 **NR**; Baron 2013 **NR**; Woolf 2011 **NR**). 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. As a result of the increased excitability of central nociceptive neurons, their threshold for activation is reduced. In this situation, pain can occur in response to low-intensity previously nonpainful stimuli (ie allodynia) and sensitivity spreads beyond the area of tissue injury (ie secondary hyperalgesia) (Sandkuhler 2009 **NR**). Wind-up, LTP and secondary hyperalgesia may all contribute to central sensitisation and may share some of the same cellular mechanisms but are independent phenomena.

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 2018 **NR**; Simonetti 2013 **NR**). Unique patterns of either upregulation or downregulation of neuropeptides, G-protein coupled receptors, growth factors and their receptors, and many other signalling 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 activity in neurons, central neuroinflammation involving surrounding glial and immune cells (including microglia) can also modulate synaptic transmission (Baral 2019 **NR**; Ji 2018 **NR**). Strong evidence has accumulated to suggest glial and neuroimmune mechanisms contribute to sex differences in pain (Mapplebeck 2017 **NR**).

1.1.2.3 | Central projections of nociceptive pathways

Different qualities of the overall pain experience are subserved by five major ascending spinal cord projection pathways; the spinothalamic, spinoreticular, spinomesencephalic, cervicothalamic and spinohypothalamic pathways. 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 (Craig 2003 **NR**). This pathway provides information on the sensory-discriminative aspects of pain (ie the site and type of painful stimulus). The spinoreticular and spinomesencephalic (spinoparabrachial) tracts project to the medulla and midbrain 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 (Kobayashi 2012 **NR**; Craig 2009 **NR**; Price 2000 **NR**). Many of the second-order projection neurons in these pathways are superficial dorsal horn lamina I neurons that express the NK1 receptor and are stimulated by peptidergic C-fibre afferents (Todd 2010 **NR**). Other connections include those to 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 that are important for the regulation of descending pathways to the spinal cord. Descending projections from the medullary dorsal reticular nucleus (DRt) are important in facilitating the diffuse noxious inhibitory control (DNIC) (see Figure 1.1) (Treede 2016 **NR**; Ossipov 2010 **NR**; Tracey 2007 **NR**).

Figure 1.1 | The main ascending and descending spinal nociceptive pathways
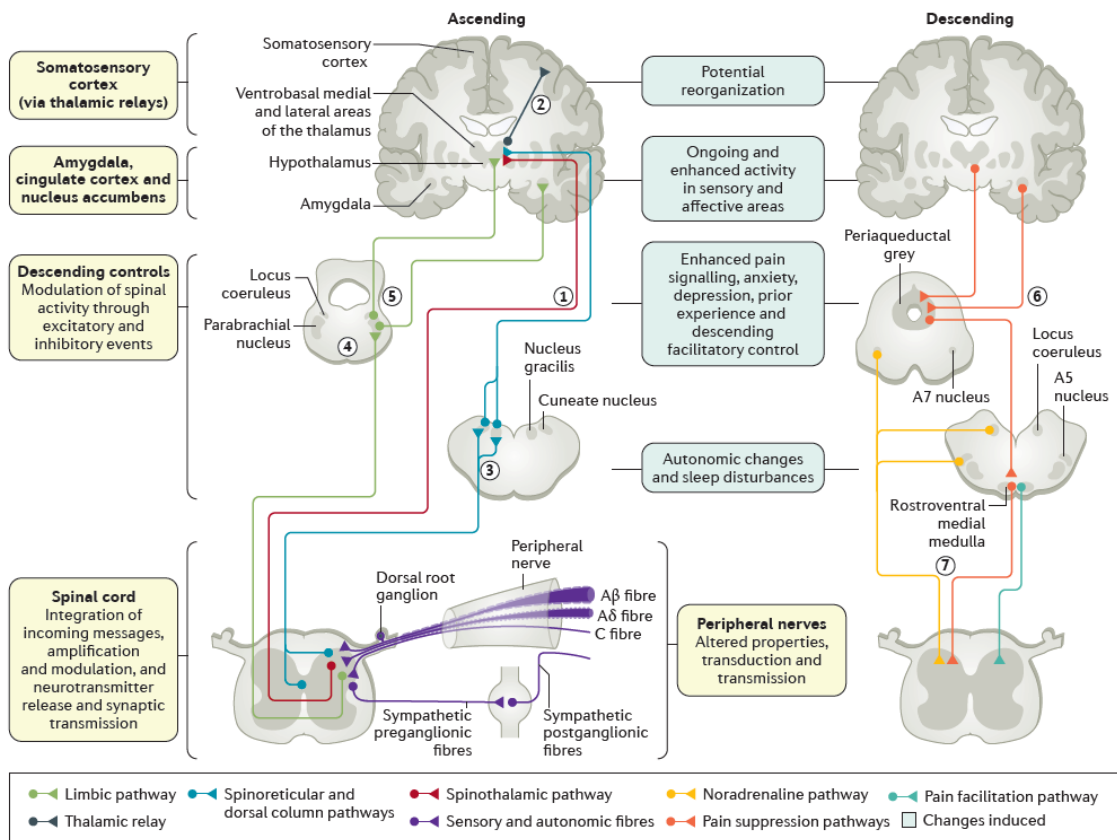
In the ascending afferent pathways, the sensory components of pain are via the spinothalamic pathway to the ventrobasal medial and lateral areas ①, which then project to the somatosensory cortex allowing for the location and intensity of pain to be perceived ②. The spinal cord also has spinoreticular projections and the dorsal column pathway to the cuneate nucleus and nucleus gracilis ③. Other limbic projections relay in the parabrachial nucleus ④ before contacting the hypothalamus and amygdala, where central autonomic function, fear and anxiety are altered ⑤. Descending efferent pathways from the amygdala and hypothalamus ⑥ drive the periaqueductal grey, the locus coeruleus, A5 and A7 nuclei and the rostroventral medial medulla. These brainstem areas then project to the spinal cord through descending noradrenaline (inhibition via α2 adrenoceptors) and, in neuropathy, there is a loss of this control and increased serotonin descending excitation via 5-HT3 receptors ⑦. The changes induced by peripheral neuropathy on peripheral and central functions are shown.
Reproduced with permission from Colloca 2017.

1.1.2.4 | Descending modulatory pathways

The brain has a remarkable capacity to modulate pain according to the competing demands of physiological, psychological and social factors. The neural contributors to this modulation are complex and only partly elucidated. Best understood is a descending pain-modulatory circuit that projects to the spinal cord and changes the experience of pain by directly or indirectly modulating (inhibiting or facilitating) nociceptive traffic (Ossipov 2010 **NR**). Descending pathways contribute to the modulation of nociceptive transmission in the spinal cord via presynaptic actions on primary afferent fibres, postsynaptic actions on projection neurons or via effects on interneurons within the dorsal horn. Sources include direct corticofugal and indirect (via

modulatory structures such as the PAG) pathways from the cortex and from 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 (Ossipov 2010 **NR**). The relative balance between descending inhibition and facilitation varies with the type and intensity of the stimulus and also with time following injury (Chen 2019 **NR**). Serotonergic and noradrenergic pathways in the dorsolateral funiculus (DLF) contribute to descending inhibitory effects and serotonergic pathways have been implicated in facilitatory effects (Bannister 2017 **NR**).

Inhibitory modulation occurs within the dorsal horn and can be mediated by non-nociceptive peripheral inputs, local inhibitory gamma-amino butyric acid (GABA) and glycine interneurons, descending bulbospinal projections and higher-order brain function (eg distraction, cognitive input). These inhibitory mechanisms are activated endogenously through neurotransmitters such as endorphins, enkephalins, noradrenaline (norepinephrine) to reduce the excitatory responses to persistent C-fibre activity. Serotonin (5-HT) has been implicated as both pronociceptive and inhibitory (Bannister 2017 **NR**).

Similar mechanisms are the basis of many exogenous analgesic agents (Bannister 2017 **NR**; Ossipov 2010 **NR**; Sandkuhler 2009 **NR**). Thus, analgesia may be achieved by either enhancing inhibition (eg opioids, clonidine, antidepressants) or by reducing excitatory transmission (eg local anaesthetics, ketamine) (Yekkirala 2017 **NR**).

A feature of sensory processing is that not all of the signals received from receptors are perceived. The limited processing capacity of the brain is optimised by prioritising behaviourally relevant signals, while suppressing less important signals. Advances in human functional brain imaging have provided new evidence of how pain perception is shaped by other sensory modalities and attentional or emotional processing by the cerebral cortex and basal forebrain (Wager 2015 **NR**; Carlino 2014 **NR**). The engagement of attention, expectation and reappraisal mechanisms provides for complex cognitive modulation of pain (Bushnell 2013 **NR**; Wiech 2013 **NR**). This is the basis of placebo-induced analgesia (see Section 1.3) and for using psychological interventions to target endogenous pain modulation (Flor 2014 **NR**; Carlino 2014 **NR**).

1.1.3 | Physiological and pathological pain

As discussed in the introduction, pragmatic working clinical definitions of acute and chronic pain continue to be time-based and do not explicitly identify underlying pathophysiology. However, the development of mechanism-based functional classification schemes and identification of clinically useful pain biomarkers continue to be intensively researched (Tracey 2019 **NR**; Vardeh 2016 **NR**).

The basic framework most commonly used addresses heterogeneity of pain by identifying "nociceptive" and "inflammatory" classes of physiological or adaptive pain, together with "neuropathic" and "CNS dysfunctional (nociplastic)" classes of pathological or maladaptive pain (Tracey 2019 **NR**; Kosek 2016 **NR**; Vardeh 2016 **NR**; Woolf 2010 **NR**). Nociceptive and inflammatory pain are considered to be physiological functions of the nociceptive division of the somatosensory nervous system, which monitors the physical state of the body (Sommer 2018 **NR**). It has been understood from the earliest investigations by Sherrington and later landmark studies by Wall and Melzack that this system does not simply locate and measure the intensity of painful sensory stimulation; it also encodes innate aversive reinforcing signals that drive motivational, emotional and cognitive processing in the brain (as described below) (Seymour 2019 **NR**). In humans and other animals, these systems support escape and defensive behaviours that minimise potential lethal tissue damage, as well as coping behaviours that manage recovery from

such damage and avoidance behaviours that use learning signals to minimise the risk of such damage in the future (Seymour 2019 **NR**). This broad functionality can be shown to engage most of the major functional brain subdivisions (Tracey 2019 **NR**). Their basic physiological importance is shown by the unavoidable tissue damage suffered in humans with rare genetic mutations that render them insensitive to pain (Dib-Hajj 2019 **NR**).

Neuropathic pain is defined as "*pain caused by a lesion or disease in the somatosensory nervous system*" (Scholz 2019 **GL**; Jensen 2011 **GL**). The estimated prevalence of neuropathic pain is much higher than commonly thought and in the range of 7–10% of the population (van Hecke 2014 **NR**). Although commonly regarded as 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 (APS) patients (Hayes 2002 **Level IV**). Similarly, acute medical conditions may present with neuropathic pain (Gray 2008 **NR**) (as discussed further in Section 8.1.4). Nerve injury and associated alterations in afferent input or hyperexcitability associated with central pain (eg caused by stroke, spinal cord injury [SCI], multiple sclerosis) can induce structural and functional changes at multiple points in nociception pathways with complex long-term psychobiological consequences (Alles 2018 **NR**; Colloca 2017 **NR**; Treede 2016 **NR**; von Hehn 2012 **NR**).

CNS dysfunctional pain syndromes such as migraine, fibromyalgia and chronic pelvic pain show chronicity that often cannot be reliably linked to clinical pathophysiology in the somatosensory system (Woolf 2010 **NR**). Historically, many terms have been used to refer to clinical CNS dysfunctional pain, including "functional pain syndromes", "maldynia", or "neuroplastic" (Mayer 2009 **NR**). The IASP, however, has recently endorsed "nociplastic pain", defined as "*Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain*" (IASP 2019a **GL**; Kosek 2016 **NR**).

When viewed from this perspective, acute pain will most commonly be linked to nociceptive and inflammatory pain but also to less common neuropathic pain. It is clear, however, that the clinical definition will also capture early stages of chronicity that could lead to neuropathic and nociplastic pain in some patients. It is important to recognise that it is currently not possible to identify in advance specific patients who will undergo this transition (Kent 2019 **NR**). The probability of chronic pain developing is subject to the influences of genetic and physiological factors and how these interact with the accumulated psychological and social experiences of pain (Borsook 2018 **NR**; Flor 2014 **NR**; Denk 2014 **NR**). How these combine will determine how individuals experience pain and is also highly likely to determine their underlying resilience in coping with this experience (Bushnell 2013 **NR**; Elman 2013 **NR**) (see Sections 1.2, 1.4 and 1.5).

1.2 | Psychological aspects of acute pain

A new definition of pain has been proposed by the IASP: "*An aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury*." (IASP 2019b). The revised definition is broadened to include non-verbal presentations (eg in people with communication deficits and animals). A key part of the definition is the recognition that pain is an experience that has emotional and sensory components (ie it is not just a sensation).

This section emphasises several important points:
- Pain is always a personal experience that is influenced to varying degrees by biological, psychological and social factors;
- Pain and nociception are different phenomena – the experience of pain cannot be deduced from activity in sensory pathways;
- Through their life experiences, individuals learn the concept of pain;
- A person's report of an experience as pain should be respected;
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.

There is a consensus view that pain is an individual, multifactorial experience influenced, among other things, by culture, previous pain experience, beliefs, expectations, mood and ability to cope. Pain may be an indicator of tissue injury but may also be experienced in the absence of, or out of proportion to an identifiable tissue injury, especially when it becomes chronic. The degree of pain and disability experienced in relation to similar tissue injury varies between people; likewise, there is individual variation in response to methods to alleviate pain (Flor 2012 **NR**).

Factors that might contribute to the individual's pain experience include somatic (physical) and psychological factors as well as contextual factors, such as situational and cultural characteristics. Pain expression, which may include facial expressions, body posture, language, vocalisations and avoidance behaviour, partially represents the complexity of the psychological experience but is not equivalent to it (Kunz 2004 **Level III-2 EH**, n=40; Vervoort 2009 **Level IV EH**, n=62). Engel's enunciation (Engel 1997 **NR**) of a biopsychosocial model of illness has provided a framework for considering pain phenomena.

Biopsychosocial models of pain (Turk 1995 **NR**) are based on the proposition that psychobehavioral processes are mediated via neurobiological processes and that they interact. Biological factors are reflected in physiological and neurophysiological changes in the body and 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 (Flor 2002 **Level III-2**, n=60). At the same time, the model also proposes that psychological and social factors can affect biological processes (eg hormonal/stress responses, endogenous pain regulation) and brain structures associated with the exacerbation and maintenance of pain symptoms (Turk 2018 **NR**).

1.2.1 | Psychological factors

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

Importantly, psychological factors that contribute to the experience and impact of pain (acute or chronic) can be amenable to change and thus influence outcomes for the individual (Nicholas 2011 **NR**).

1.2.1.1 | 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 (Legrain 2012 **NR**; Eccleston 1999 **NR**). The degree to which pain may interrupt attention depends on factors such as the intensity of pain, its novelty, unpredictability, degree of awareness of bodily information, threat value, catastrophic thinking, presence of emotional arousal, environmental demands (such as task difficulty) and emotional significance.

Concepts like somatosensory amplification and hypervigilance have been used to describe the selective attention of patients towards pain to the detriment of more functional activities. These processes have been characterised as attentional bias (ie the preferential allocation of attention to information that is related to pain) and this has been extensively studied in relation to acute, chronic and experimentally induced pain. The most recent meta-analysis of this literature indicated that attentional bias appears to relate more towards the sensory aspects of the pain experience, rather than the emotional content (Todd 2018 **Level IV SR**, 52 studies, n=4,466). It is important to note that these studies may not be completely representative of clinical acute pain (eg postsurgical pain). The role of attentional mechanisms in pain experience and impact is not uniform and terms like "hypervigilance" should not be used loosely as other processes, particularly emotional ones (eg sense of threat), are likely to be involved as well as attention.

1.2.1.2 | Learning processes

The role of learning processes 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 conditioned by their consequences and this effect can be reflected in measures of associated skin conductance responses, facial activity and cortical responses (Jolliffe 2004, **Level III-2 EH**, n=46; Flor 2002 **Level III-2**, n=60). Taken together, these studies provide support for the thesis that the experience of pain is not solely due to noxious input but that environmental reinforcement contingencies can also influence this experience (see also Section 1.3).

Learning processes have also been implicated in the development and maintenance of chronic pain (Flor 2012 **NR**).

1.2.1.3 | Beliefs and 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 2007 **NR**). From this perspective, appraisals of internal and external stimuli as threats (eg catastrophising), negative affectivity and anxiety sensitivity can 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.

Studies with a range of patient samples have confirmed that thinking styles that are overly pessimistic, ruminative and helpless (eg catastrophic thinking) are frequently associated with more severe acute pain and associated distress, as well as persisting pain.

In patients who underwent anterior cruciate ligament repair, those with high Pain Catastrophising Scale (PCS) scores assessed prior to surgery reported more pain immediately after surgery and when walking at 24 h compared with those with low scores; however there was no difference in analgesic consumption (Pavlin 2005 **Level IV**, n=48). After breast surgery, catastrophising was associated with increased pain intensity and analgesic use (Jacobsen 1996 **Level IV**, n=59) and after abdominal surgery (Granot 2005 **Level IV**, n=38) and Caesarean section with higher pain scores (Strulov 2007 **Level IV**, n=47). Preoperative PCS scores also predicted pain after total knee arthroplasty (TKA) in the postoperative period (Roth 2007 **Level IV**). After a wide range of surgical procedures , the most important predictors of pain severity up to 5 d following surgery were surgical fear and pain catastrophising (beside preoperative pain and expected pain) (Sommer 2010 **Level IV**, n=1,490). In a clinical sample of aged patients, attentional avoidance of emotionally aversive stimuli prior to surgery predicted acute postoperative pain, measured by the consumption of opioids via patient-controlled analgesia (PCA) (Lautenbacher 2011 **Level IV**, n=58). This measure was a better predictor of postoperative pain than depression, anxiety and pain catastrophising. Subsequently, a systematic review of studies of psychological factors associated with acute postsurgical pain confirmed the most significant correlates are: pain catastrophising, expectation of pain, anxiety (state and trait), depression, optimism, negative affect and neuroticism/psychological vulnerability (Sobol-Kwapinska 2016 **Level IV SR** [PRISMA], 53 studies, n=10,749). This meta-analysis suggests that pain catastrophising is the most strongly associated with acute postsurgical pain (r=0.41; 95%CI 0.28 to 0.52) (see also Section 1.4).

A significant association between anxiety or pain catastrophising and the subsequent development of chronic postsurgical pain (CPSP) was reported in a systematic review in 16 of 29 studies (Theunissen 2012 **Level III-2 SR**, 29 studies, n=6,628). Following TKA, a systematic review found catastrophising is the strongest predictor of chronic pain (Lewis 2015 **Level IV SR**, 32 studies, n=29,993). Another systematic review found patients with acute and subacute back pain with high levels of catastrophising complained of more pain and disability at 6 mth and more disability at 1 y than those with low levels (Wertli 2014a **Level III-2 SR**, 16 studies, n unspecified).

High fear avoidance beliefs in patients with back pain of <6 mth duration are associated with poor outcomes, which may be improved by treatment approaches aimed at fear avoidance (Wertli 2014b **Level I** [PRISMA], 17 RCTs, n=1,153). Early postoperative fear of movement also predicted pain, disability and physical health 6 mth after spinal surgery for degenerative conditions (Archer 2014 **Level III-2**, n=141).

1.2.1.4 | Depression and anxiety

Anxiety and depression have repeatedly been found to contribute to the experience and impact of both acute and chronic pain.

Significant preoperative predictors of poor postoperative pain control included younger age (OR 1.18; 95%CI 1.05 to 1.3) (14 studies), female sex (OR 1.29; 95%CI 1.17 to 1.43) (20 studies), smoking (OR 1.33; 95%CI 1.09 to 1.61) (9 studies), history of depressive symptoms (OR 1.71; 95%CI 1.32 to 2.22) (8 studies), history of anxiety symptoms (OR 1.22; 95%CI 1.09 to 1.36) (10 studies), sleep difficulties (OR 2.32; 95%CI 1.46 to 3.69) (2 studies), higher body mass index (OR 1.02; 95%CI 1.01 to 1.03) (2 studies), presence of preoperative pain (OR 1.21; 95%CI 1.10 to 1.32) (13 studies) and use of preoperative analgesia (OR 1.54; 95%CI 1.18 to 2.03) (6 studies) (Yang 2019 **Level IV SR** [PRISMA], 33 studies, n=53,362). Interestingly, pain catastrophising, American Society of Anesthesiologists (ASA) status, chronic pain, marital status, socioeconomic status, education, surgical history, preoperative pressure pain tolerance and orthopaedic surgery (vs abdominal surgery) were not associated with increased odds of poor pain control.

Anxiety is one of the most significant predictive factors (in addition to pre-existing pain, age and type of surgery) for the severity of postoperative pain (Ip 2009 **Level IV SR**, 48 studies, n=23,037). Psychological distress (besides type of surgery and age) is the most significant predictor of postoperative analgesic consumption, not sex as is commonly believed.

Among other factors, preoperative anxiety predicted pain intensity 48 h after hysterectomy for benign conditions (Pinto 2012 **Level IV**, n=203). Subsequent multivariable analysis revealed that pain catastrophising acted as a full mediator between presurgical anxiety and postsurgical pain intensity. In the late phase after leg injury, anxiety has the only significant relationship to pain (Castillo 2013 **Level IV**, n=545). Anxiety predicted pain over all time periods: 3 to 6 mth (standardised regression weights [SRW] 0.11), 6 to 12 mth (SRW 0.14) and 12 to 24 mth (SRW 0.18).

In opioid-tolerant patients, the anxiety and autonomic arousal associated with withdrawal (Tetrault 2008 **NR**) may also have an impact on acute pain experience and report (see Section 9.7 for further details).

There is a consistent association between chronic postsurgical pain and depression as well as psychological vulnerability and stress (Hinrichs-Rocker 2009 **Level IV**, 50 studies, n≈25,000). Similarly, there is a strong relationship between persistent knee pain and depression (with higher levels of knee pain being positively related to higher levels of depression) but not with anxiety and poor mental health in general (Phyomaung 2014 **Level IV SR**, 16 studies, n=15,113).

1.2.1.5 | Implications

The presence of modifiable psychological factors, especially anxiety, catastrophising and depression, should be considered in acute pain settings and, if identified, should be targeted by treatment. The results of research evaluating psychological interventions for these factors are considered elsewhere (see Section 7.1). These psychological contributors to higher pain levels and interference in daily activities are not universal and there is considerable variability between individuals.

1.2.2 | Patient-controlled analgesia

In general, anxiety seems to be the most important psychological variable that affects PCA bolus use. Preoperative anxiety correlates with increased postoperative pain intensity, the number of PCA demands made by the patient (often "unsuccessful" presses during the lockout interval), degree of dissatisfaction with PCA and lower self-reports of quality of analgesia (Thomas 1995 **Level III-1**, n=110; De Cosmo 2008 **Level IV**, n=80; Hsu 2005 **Level IV**, n=40; Ozalp 2003 **Level IV**, n=99; Brandner 2002 **Level IV**, n=71; Perry 1994 **Level IV**, n=99; Jamison 1993 **Level IV**, n=68). Another study designed to look at predictors of PCA demands made during the lockout interval also found that anxiety and negative affect positively predicted unsuccessful PCA demands and postoperative pain, as did preoperative intrusive thoughts and avoidant behaviours about the impending surgery (Katz 2008a **Level IV**, n=117).

Evidence regarding PCA opioid consumption and psychological variables is however contradictory, with some studies showing no change (Jamison 1993 **Level IV**, n=68; Gil 1992 **Level IV**, n=50; Gil 1990 **Level IV**, n=80) and others showing an increase in analgesia demands (Katz 2008a **Level IV**, n=117; De Cosmo 2008 **Level IV**, n=80; Ozalp 2003 **Level IV**, n=99).

In a study looking at the effect of a number of psychological factors on both pain and IV morphine use (by PCA) in the immediate postoperative period, and on pain 4 wk after surgery, preoperative self-distraction and 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 wk after surgery (Cohen 2005 **Level IV**, n=122).

There was no relationship between locus of control and postoperative pain intensity, satisfaction with PCA or PCA dose-demand ratio (Brandner 2002 **Level IV**, n=71). Preoperative depression was associated with increased pain intensity, opioid requirements, PCA demands and degree of dissatisfaction (Hsu 2005 **Level IV**, n=40; Ozalp 2003 **Level IV**, n=99) (for further details on PCA see also Section 6.0).

KEY MESSAGES

1. High pain-related fear avoidance beliefs in patients with back pain of less than 6 months duration are associated with poor outcomes, which may be improved by treatment approaches aimed at fear avoidance (**U**) (**Level I** [PRISMA]).

2. There is a significant association between high levels of catastrophising in acute and subacute back pain and pain and disability at later points of time (**U**) (**Level III-2 SR**).

3. Psychological factors associated with poor postoperative pain control are in particular anxiety (state and trait) and catastrophising, but also expectation of pain, depression, negative affect and neuroticism/psychological vulnerability (**S**) (**Level IV SR** [PRISMA]).

4. There is significant association between anxiety, pain catastrophising (**U**) (**Level III-2 SR**), depression, psychological vulnerability and stress (**U**) (**Level IV SR**) and the subsequent development of chronic postsurgical pain.

5. 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 | Placebo and nocebo effects in acute pain

The study of placebo is directly relevant to the field of pain management, as it provides further understanding of the mind–brain interaction in the modulation of pain and is a core element of routine clinical management (Finniss 2010 **NR**).

The term "placebo", originally defined as an inert substance having therapeutic response, has been used in the medical literature for over 200 y. Only in the last 50 y, however, has interest grown in responses to placebo administration. The first major systematic review of the topic showed a placebo effect for many interventions but particularly for those interventions aimed at analgesia (Beecher 1955 **Level I**, 15 RCTs, n=1,082). The early studies included in this systematic review of response to placebo were mainly studies of placebo vs active medicine or intervention alone without a control no-treatment group (nonplacebo group).

Placebo effects are psychobiological effects that are attributable to the psychosocial context (or treatment ritual) surrounding the patient. Importantly, these genuine effects must be distinguished from other causes of improvement following administration of a placebo (placebo responses), such as spontaneous remission, regression to the mean and the natural history of acute pain (Price 2008 **NR**). Defining placebo and placebo effects has been difficult, primarily due to the traditional definition, which uses the word "inert", therefore theoretically rendering it as being unable to have any power to elicit an effect (Moerman 2002 **NR**). Recent reconceptualisations of placebo effects have emphasised several key points which are highly relevant to modern pain management practice (Finniss 2010 **NR**; Miller 2008 **NR**).

- Placebo responses refer to all health changes following administration of an inert agent (including natural history and regression to the mean) (Evers 2018 **NR**).
- Placebo effects are changes attributable to specific psychobiological mechanisms, whether a traditional placebo is given or as part of a routine clinical interaction (Evers 2018 **NR**).
- The key aspect of placebo administration is the act of simulating a treatment context or ritual, regardless of the content of the placebo.
- Routine clinical care occurs in a rich therapeutic context and, on this basis, placebo effects exist in everyday practice even though no traditional placebo is given. The overall outcome of a treatment is related to both the treatment itself and the context in which it is given (the component attributable to placebo effects).

The term "nocebo" has been used to express the opposite (negative) response following placebo administration, particularly in relation to development of adverse effects from interventions or, in the case of painful stimuli, with an increased pain response expressed. Nocebo studies in pain show moderate to large nocebo effects of high variability (Petersen 2014 **Level I** [PRISMA], 10 RCTs, n=619). The results are similar to those seen for placebo effects; combinations of verbal suggestions and conditioning (see below) are more effective than verbal suggestions alone. The authors suggest that these results demonstrate "*the importance of minimising nocebo effects in clinical practice*".

1.3.1 | Mechanisms

The study of placebo mechanisms has traditionally been divided into psychological and neurobiological categories, although it is the interplay between the two that is the key to the topic area.

1.3.1.1 | Psychological mechanisms

There are many psychological mechanisms of placebo effects proposed, including expectation, conditioning, learning, reward and anxiety reduction (Price 2008 **NR**).

Expectancy

Expectancy has been one of the most studied psychological mechanisms and relates to patient expectations of a future response. Expectancy can result in increased pain response to nociceptive stimuli as well as a placebo response to an analgesic intervention (Atlas 2012 **NR**). It has been associated with placebo effects in studies, where verbal cue ranges from a simple instruction "*this is a powerful painkiller*" (Price 1999 **Level II**, n=40, JS 4) to the use of conditioning protocols to maximise expectancy (Voudouris 1989 **Level II**, n=20, JS 4; Voudouris 1990 **Level III-1**). Furthermore, a "graded" effect can be seen in studies with variable levels of expectancy (such as the classic "double-blind" instruction, which carries a 50% uncertainty) to more certain information about treatment expectations "*the drug I will give you is a powerful painkiller*" (Vase 2003 **Level II**, n=13, JS 4; Verne 2003 **Level II**, n=10, JS 4; Pollo 2001 **Level II**, n=38, JS 3). More recently, in the setting of chronic low back pain, expectancies were associated with duration and stability of placebo effects following diagnostic injections (Finniss 2019 **Level II**, n=107, JS 5). This underscores the dynamic nature of the construct and emphasises the role of repeated expectancy assessment and modulation over the duration of a healthcare encounter.

Treatment expectations are also involved in studies of the open-hidden paradigm (Finniss 2010 **NR**). Giving a treatment "hidden", without the patient's knowledge (eg by a computerised pump behind a curtain) and comparing the effects when the same treatment is given "open" (in the usual therapeutic context with a health professional present) has shown that open administration of a range of analgesics is, by far, more effective than hidden administration. This approach permits measurement of the placebo effect as "*the difference in effect between the open and hidden administration*". An example of such a trial compared the efficacy of a remifentanil infusion (0.8 ng/mL effect site concentration) on experimental pain in volunteers under three conditions (Bingel 2011 **Level III-3 EH**):
- without expectation of analgesia (hidden administration);
- with expectancy of a positive analgesic effect (open administration by a clinician); and
- with negative expectancy of analgesia (claimed discontinuation of analgesic infusion while infusion continued).

The pain relief achieved by hidden administration of remifentanil was more than doubled by the open administration and completely negated by the claimed discontinuation of the infusion. Functional MRI (fMRI) showed that, during positive expectancy, activity in the endogenous pain modulatory system was increased, while negative expectancy increased activity in the hippocampus.

These findings and the results of other groups suggest that RCTs comparing an analgesic with a placebo may underestimate the efficacy of the analgesic (Lund 2014 **Level II EH**, n=48 [cross over], JS 5). The hypothesis that placebo effect and drug effect are additive, upon which calculation of efficacy is based, is most likely flawed. This is particularly true when the placebo effect is large. Expectations influence placebo and nocebo response to acute pain independently from personality factors (Corsi 2017 **Level III-1 EH**)

In conclusion, expectancy is a powerful determinant of placebo response, with only minor changes in the way information is delivered to the patient having the ability to significantly alter expectancy and the magnitude of the placebo effects.

Classical conditioning

Classical conditioning is a learning phenomenon whereby repeated associations between a neutral stimulus and an active treatment (unconditioned stimulus) can result in the ability of the neutral stimulus itself being able to elicit an effect similar to that of the unconditioned stimulus (Finniss 2010 **NR**). Typically, an opioid analgesic is given on repeated occasions and then replaced with a placebo-treatment simulation. These phenomena have been demonstrated in animals (Pacheco-Lopez 2006 **BS**) and in humans (Voudouris 1989 **Level II EH**, n=20, JS 4; Voudouris 1990 **Level III-1 EH**). In a similar way, treatment history can influence the efficacy of a subsequent treatment (Kessner 2014 **Level III-2 EH**). In an experimental setting, induced negative experience with a first treatment resulted in reduced response to a second analgesic treatment; the size of the effect was modulated by psychological trait variables such as anxiety, depression and locus of control. There is evidence that social or observational learning may also be a determinant of placebo effects (Colloca 2006 **Level III-1 EH**). For example, placebo effects were larger in subjects who had higher empathy after witnessing another volunteer in pain (Colloca 2009 **Level II EH**, n=48, JS 2).

1.3.1.2 | Neurobiological mechanisms

Studies into placebo analgesia have provided a substantial component of the knowledge about placebo mechanisms, although it is now known that there are multiple placebo effects that operate across many different medical conditions (Benedetti 2008 **NR**).

At a biochemical level, pioneering studies have shown that placebo effects in acute pain are either completely or in part mediated by endogenous opioids, by virtue of their reversibility with naloxone (Benedetti 1995 **Level II EH**, n=47, JS 3; Levine 1978 **Level II EH**, n=93, JS 3). The role of cholecystokinin (CCK) was demonstrated through the potentiation of placebo effects using a CCK antagonist (proglumide) (Benedetti 1995 **Level II EH**, n=93, JS 3). Interestingly, CCK has also been shown to be responsible for nocebo effects and this suggests that anxiety and panic mechanisms (also associated with CCK release) may be activated (Benedetti 2007 **NR**).

Using both conditioning and expectancy manipulations with the administration of an opioid analgesic, the resulting placebo effect was mediated by endogenous opioids (Amanzio 1999 **Level II EH**, n=229, JS 3). In contrast, in patients who received a nonopioid analgesic during conditioning, the placebo effect was not reversed by naloxone. These findings are a powerful demonstration that there is not one placebo effect but many. One mechanism for this nonopioid-mediated placebo analgesia was found to be the endogenous cannabinoid system (cannabinoid type 1 [CB_1] receptor) (Benedetti 2011 **Level III-1 EH**).

The neuroanatomy of placebo analgesic effects has been partially unravelled. A positive emission tomography (PET) study demonstrated similar brain changes to placebo as seen with opioid administration (Petrovic 2002 **Level III-2 EH**). Further PET and fMRI studies have supported the involvement of key regions of the brain associated with opioid analgesia (Zubieta 2005 **Level III-3 EH**), including subcortical (Bingel 2006 **Level III-2 EH**) and spinal cord mechanisms (Eippert 2009 **Level III-1 EH**). Taken together, these studies show growing neurobiological evidence of placebo-induced brain and spinal cord modulation of pain, although much more research is needed in this area.

A meta-analysis of 25 neuroimaging studies identified that placebo analgesia and expectancy-based pain modulation resulted in reductions of activity in brain regions involved in pain processing (eg the dorsal anterior cingulate, thalamus and insula) (Atlas 2014 **Level IV EH SR**). Other regions with reduced activity were the amygdala and the striatum; as these are related to affect and valuation, placebo effects involve these components too. In addition, regions such as the prefrontal cortex, the midbrain surrounding the PAG and rostral anterior cingulate showed increased activity with expectations for pain reduction.

There is a link between polymorphisms in the dopamine, opioid and endocannabinoid genes and response to placebo, demonstrating potential genetic determinants of placebo effects (Colloca 2019 **Level III-2 EH**, n=160).

1.3.2 | Clinical findings

Many meta-analyses include studies that also have a control nonplacebo/nocebo group. One of these reveals a relatively small placebo effect size for all clinical conditions (60 assessed) (Hrobjartsson 2010 **Level I** [Cochrane], 234 RCTs, n unspecified), but did not consider nocebo. The majority of studies measured continuous outcomes (158 RCTs, n=10,525) but the results are also consistent in those assessing binary outcomes (44 RCTs, n=6,041). In the studies with continuous outcomes, there is an effect of placebo treatment (SMD -0.23; 95%CI -0.28 to -0.17) (158 RCTs, n=10,525), which is larger for patient-reported (SMD -0.26; 95%CI -0.32 to -0.19) (109 RCTs, n=8,000) than for observer-reported outcomes (SMD -0.13; 95%CI -0.24 to -0.02) (49 RCTs, n=2,513). Overall, larger placebo effects are seen with physical placebo interventions (eg acupuncture), patient-involved outcomes, smaller trials and trials that did not inform patients about the possible placebo intervention.

Importantly, trials aimed at studying placebo effects (rather than assessing responses in placebo-control groups) demonstrate larger placebo effects, particularly in the case of analgesia (Vase 2002 **Level I**, 37 RCTs, n=2,298). Effect sizes can be five times higher in these studies than in analysis of placebo effects on control groups, demonstrating an important difference when understanding placebo effects in clinical trials (where instructions are uncertain and the context does not replicate routine clinical care) (Vase 2009 **Level I** [QUOROM], 24 RCTs, n=602). Consistently positive but highly variable placebo responses are obvious in studies involving analgesia specifically (pooled SMD -0.28; 95%CI -0.36 to -0.19) (60 RCTs [continuous outcome, pain], n=4,154) with a wide range of response in the individual trials from around SMD -1.0 to 0.5. This variability is also seen in targeted studies on placebo (Vase 2009 **Level I** [QUOROM], 24 RCTs, n=602).

1.3.3 | Clinical Implications

The clinical implications of placebo effects are widespread and there is much more research needed to understand how placebo effects operate and how they can be manipulated in clinical practice. However, the notion that placebo effects (and therefore mechanisms) may be a component of routine pain management practice is highly important (Klinger 2014 **NR**; Finniss 2009 **NR**). If one can study how psychosocial factors alter the patient's nociception and the experience of pain (by running experiments in which placebos are given), this has direct implications for clinical care where, even though no placebo is given, placebo effects are present.

In recent times, the ethical debate has shifted somewhat as the concept of placebo is better understood. It is widely accepted that placebos should not be administered in a deceptive manner (Finniss 2010 **NR**; Brody 1982 **NR**). However, there are not the same ethical problems associated with harnessing the placebo effects that coexist with routine "active" treatments, as the outcome of a treatment is attributable to both the treatment itself and the specific context in which it was given (the placebo component). An applied example is that of the PSYHEART trial, where a specific pre-treatment intervention addressing patients expectations pre-cardiac surgery resulted in significant reductions in biological markers (endocrine and immune markers of stress), reduced disability and improved quality of life at 6 mth post-surgery (Rief 2017 **Level II**, n=124, JS 5).

It is suggested that, in a therapeutic interaction, the placebo effect can be clinically utilised by enhancing expectations and using learning components (Klinger 2014 **NR**). Practical examples of this are listed below.

To enhance expectations:

- Assess and manage expectations over the entire time course of a treatment;
- Emphasise positive effects of medicines;
- Avoid stressing adverse effects;
- Explain effects and mechanisms of action of medicines;
- Interact personally with the patient;
- Do not rely only on written handouts; and
- Avoid unrealistic expectations.

To enhance learning components:

- Administer analgesics in an open manner;
- Connect the administration to positive internal states and external conditions;
- Combine analgesics with other pain-relieving approaches, preferably with time-contingent administration of analgesics; and
- Reinforce positive and minimise negative experiences.

KEY MESSAGES

1. Responses to placebo across all clinical conditions are small but consistently positive. They are more prominent, although highly variable in magnitude, in studies of pain (**U**) (**Level I** [Cochrane Review]).

2. Nocebo effects in studies of pain are of moderate to large size and of high variability (**U**) (**Level I** [PRISMA]).

3. Trials aimed at studying placebo effects demonstrate larger placebo effects than those assessing responses in placebo-control groups (**U**) (**Level I** [QUOROM]).

4. Analgesic placebo effects are based upon multiple neurobiological mechanisms, including involvement of endogenous opioid, cholecystokinin (**U**) (**Level II**), endogenous cannabinoid systems (**U**)(**Level III-1**) and genotype (**N**) (**Level III-2**).

5. Analgesic placebo effects are based upon multiple psychological determinants including expectancy, classical conditioning and social and observational learning (**S**) (**Level II**).

6. Placebo and nocebo effects have significant influence on the efficacy of analgesics (**U**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Placebo effects are the consequence of the psychosocial context (or treatment ritual) on the patient's mind, brain and body (**U**).

☑ Placebo effects occur in routine clinical care even when no traditional placebo is given. The outcome of a treatment is attributable to both the treatment itself and the contextual (or placebo) component (**U**).

☑ Nocebo effects occur in routine clinical care and are seen as an increased pain response to a painful stimulus or the development of adverse effects not caused by, or separate from, the intervention (**U**).

☑ Ethical harnessing of placebo and minimisation of nocebo effects will improve response to clinical management interventions (**U**)

1.4 | Progression of acute to chronic pain

Chronic pain is common in the community and is moderate to severe in intensity in approximately 20% of the population (Kennedy 2014 **Level IV**, n 39,400,000 [chronic pain sufferers]). This inevitably leads to significant personal and economic cost (Breivik 2006 **Level IV**, n=46,394; Deloitte Access Economics 2019 **NR**). Episodes of acute pain may result in chronic pain with subsequent impact on quality of life, employment and mental health (Steyaert 2012 **NR**; Lavand'homme 2011 **NR**; McGreevy 2011 **NR**). The prediction and prevention of transition to chronic pain may therefore convey health and economic benefits (see also Section 3.3).

The 11th revision of the International Classification of Diseases (ICD-11) defines chronic postsurgical pain (CPSP) as pain developing or increasing in intensity after a surgical procedure, in the area of the surgery, persisting beyond the healing process (ie at least 3 mth) and not better explained by another cause such as infection, malignancy, or a pre-existing pain condition (Schug 2019 **GL**).

CPSP is common and although often mild, may be of sufficient severity to interfere with function and quality of life in 1 to 10% of cases (De Kock 2009 **Level IV**). The currently accepted prevalence of CPSP is shown below, however some studies suggest the prevalence may be lower than previously thought (see Table 1.2) (Chan 2016 **Level II**, n=2,924, JS 5; Fletcher 2015 **Level IV**, n=3,120).

CPSP often has identifiable neuropathic characteristics, although this is procedure specific, and is often poorly responsive to opioids (Chan 2011 **Level II**, n=423, JS 5; Wylde 2011 **Level IV**, n=1,334; Haroutiunian 2013 **NR**; Macrae 2008 **NR**; Kehlet 2006 **NR**). The lack of efficacy of opioids for treating CPSP is one factor contributing to the current prescription opioid crisis (Neuman 2019 **NR**; Hollmann 2019 **NR**) (see also Sections 1.4.3, 8.13 and 9.7).

Other well-characterised acute pain events may also lead to chronic pain, such as post-traumatic pain (see below and Section 8.1), acute back pain (see Section 8.7) and herpes zoster (see Section 8.6.2). Although CPSP tends to be associated with major surgery, involving significant acute pain, nerve injury and inflammation, it may also occur following minor operations. The surgical drive towards minimally invasive surgery has reduced acute postsurgical pain but has had a limited effect on the incidence of CPSP (Roth 2018 **Level IV**, n=1,996; Lavand'homme 2017 **NR**).

This section will focus primarily on CPSP, although the underlying mechanisms and risk factors are also relevant to the nonsurgical conditions mentioned above.

1.4.1 | Epidemiology of chronic postsurgical pain

There is a high prevalence of CPSP and chronic pain following trauma; 22.5% of 5,130 patients attending chronic pain clinics in North Britain cited surgery as a cause for their pain and 18.7% felt that trauma was the primary cause (Crombie 1998 **Level IV**, n=5,130). As chronic pain is very common in the population and only a small percentage of people with chronic pain attend pain clinics, data obtained from clinics may not accurately reflect the scale of the problem in the community. A randomised population survey from Portugal found that only 6% of those identified with chronic pain felt that it was due to surgery (Azevedo 2012 **Level IV**, n=2,213). In contrast, a Norwegian population-based study found 40.4% prevalence of pain in the anatomical region of surgery 3 mth to 3 y later (Johansen 2012 **Level IV**, n=2,043). In 18.3% (n=373), the pain was moderate to severe. The prevalence of moderate to severe pain was reduced to 10.5% by excluding all respondents with the same pain before surgery and to 6.2% by excluding all respondents with any pain before surgery. Factors associated with CPSP were sensory abnormalities in the area of surgery (hyperaesthesia [OR 6.27; 95%CI 4.43 to 8.86] or hypoaesthesia [OR 2.68; 95%CI 1.05 to 3.50]) and psychological distress (OR 1.69; 95%CI 1.22 to 2.36).

Chronic pain following trauma is common and approximately 70% of patients without prior pain reported significant pain 6 mth following injury in one UK study (Rockett 2019 **Level II**, n=64, JS 5). Preceding studies found similar high rates of 46% to 85% of polytrauma survivors with subsequent chronic pain (Gross 2011 **Level IV**, n=229) and 72% of some pain in the last 24 h at 1 y after serious trauma (Holmes 2010 **Level III-2**, n=290).

Less is known about CPSP in the paediatric population, but it has been estimated that 20% of children experience CPSP 1 y after spinal and mixed major surgery (Rabbitts 2017 **Level IV SR**, n=628; (Williams 2017 **NR**).

The incidence of CPSP varies with the type of operation and it is particularly common where nerve trauma is inevitable (eg amputation) or where the surgical field is richly innervated (eg chest wall) (see Table 1.2) (Wylde 2011 **Level IV**, n=1,294; Macrae 2008 **NR**; Kehlet 2006 **NR**). In a prospective cross-sectional study at a university-affiliated hospital and level 1 trauma centre, 14.8% of patients described CPSP, in particular those after trauma and major orthopaedic surgery (Simanski 2014 **Level IV**, n=3,020). A similar study, focussing on neuropathic CPSP only following two procedure types, identified an incidence of 3.2% for laparoscopic herniorrhaphy vs 37.1% for breast cancer surgery at 6 mth after surgery (Duale 2014 **Level IV**, n=3,112). Overall, these data support the high incidence of CPSP and the frequent linkage of CPSP to nerve injury.

Table 1.2 | Incidence of chronic pain after surgery

Type of surgery	Any CPSP (%)	Severe CPSP (%)	Neuropathic pain (proportion)*
Abdominal surgery (visceral)	17-21%	Not reported	Not reported
Amputation	30-85%	5-10%	80%
Caesarean section	6-55%	5-10%	50%
Cholecystectomy	3-50%	Not reported	Not reported
Craniotomy	7-30%	25%	Not reported
Dental surgery	5-13%	Not reported	Not reported
Hip arthroplasty	27%	6%	1-2%
Inguinal herniotomy	5-63%	2-4%	80%
Knee arthroplasty	13-44%	15%	6%
Melanoma resection	9%	Not reported	Not reported
Mastectomy	11-57%	5-10%	65%
Sternotomy (CABG)	30-50%	4-28%	Not reported
Thoracotomy	5-65%	10%	45%
Vasectomy	0-37%	Not reported	Not reported

*CABG-Coronary artery bypass graft surgery; * assessed by screening questionnaires in most studies. Adapted from Glare 2019; Schug 2017.*

1.4.2 | Characteristics of chronic postsurgical pain

Efforts are now being made to standardise outcome measures to characterise CPSP in future RCTs and epidemiological studies (Wylde 2014 **Level IV**, n=1,294; VanDenKerkhof 2013 **GL**). CPSP may persist as a continuum from acute postsurgical pain or it may occur following a pain-free interval. CPSP may occur in the skin or deep tissues of the region of surgery, it may be referred to characteristic areas due to viscerosomatic convergence or be related to the course of a nerve injured by surgery.

A significant proportion of patients with CPSP demonstrate sensory abnormalities, suggesting that CPSP often has a neuropathic component (Johansen 2016 **Level IV**, n=81; Aasvang 2008 **Level IV**, n=46). The incidence of acute neuropathic pain has been reported as 1 to 3%, based on patients referred to an APS, primarily after surgery or trauma (Hayes 2002 **Level IV**). The majority of these patients had persistent pain at 12 mth, suggesting that acute neuropathic pain is a risk factor for chronic pain. These qualitative results were confirmed in a subsequent study (Beloeil 2017 **Level III-2**, n=593). Using a screening tool (DN-4), acute neuropathic pain was identified in 5.6% (95%CI 3.6 to 8.3) on the day of surgery and in 12.9% (95%CI 9.7 to 16.7) on POD 1. Postsurgical neuropathic pain was identified in phone follow-up 2 mth postsurgery in 33.3% of patients; acute neuropathic pain was a risk factor for its development (OR 4.2; 95%CI 2.2 to 8.1). Similarly, immediately after thoracotomy or video-assisted thoracic surgery (VATS), 8% of patients scored positively on another screening tool for neuropathic pain (LANSS) and 22% 3 mth later; again acute neuropathic pain was identified as a risk factor for chronic neuropathic pain (RR 3.5; 95%CI 1.7 to 7.2) (Searle 2009b **Level III-2**, n=100). Following VATS, sensory changes suggestive of nerve injury were demonstrated in most patients but there was no difference in sensory abnormalities or measures of central sensitisation between patients with and without CPSP (Wildgaard 2012 **Level IV**). Similarly, changes in sensory thresholds (warmth detection and heat pain) were demonstrated in most pain-free patients following open inguinal herniorrhaphy (Aasvang 2010b **Level IV**). This suggests that, although nerve injury is frequently associated with CPSP, such injury does not inevitably lead to chronic pain. It should be recognised however that numbness might still be distressing to some patients. Additionally, neuroplastic processes termed central sensitisation may occur without nerve injury and may result in altered nociceptor function with a gain (sensitisation) or a loss (desensitisation) of function of nociceptors, resulting in sensory changes superficially resembling neuropathic pain. Assessment of these sensory changes using techniques such as quantitative sensory testing may in the future lead to more individualised treatment and drug development for the prevention and treatment of CPSP (Arendt-Nielsen 2018 **NR**).

The intensity and character of CPSP is variable. Descriptors may relate to neuropathic pain (shooting, burning, tingling) (VanDenKerkhof 2013 **Level IV**) but somatic / nociceptive pain characteristics (aching, tender, stabbing, squeezing) are also commonly reported (Chan 2011 **Level III-1**), especially associated with joint arthroplasty (Wylde 2011 **Level IV**, n=1,294). Typically around 10% of patients describe the CPSP as severe, although this proportion may be higher in some surgical groups (Glare 2019 **NR**). The sequelae of CPSP vary from mild discomfort to a significant impact on quality of life. The negative impact of CPSP is similar to that of other chronic pain conditions and, along with psychological distress, may include the use of multiple analgesics, regular medical attendances, inability to undertake certain activities and difficulty returning to work (Chan 2011 **Level III-1**, n=640; Steyaert 2012 **NR**).

1.4.3 | Opioids and CPSP

In recent years, the use of strong opioids to manage acute and chronic non-cancer pain has been increasing. This has been one factor in the generation of a global opioid crisis, with opioid use

and deaths from overdose of prescription drugs increasing dramatically in many countries (Jones 2018 **NR**). Surgery is a risk factor for both persistent pain and ongoing inappropriate opioid use (Hah 2017 **NR**). Prolonged opioid use after hospital discharge seems to be relatively common, occurring in 10.5% of patients for greater than 90 d after surgery in an Australian study (Stark 2017 **Level IV**, n=970), and in 3% of opioid naïve patients at 90 d in a large cohort study from Canada (Clarke 2014 **Level IV**, n=39,140). In contrast, opioid use by outpatient pain clinics has been decreasing in chronic non-cancer pain due to lack of evidence for their efficacy (Dowell 2016 **GL**; Chou 2009 **GL**). For more details see also Section 8.13.

Not only is CPSP a risk factor for ongoing opioid use, but opioid use may trigger or worsen symptoms of CPSP (see also Section 1.4.4 below). The use of high dose opioids in the acute setting has been shown to activate neuroplastic processes which may result in CPSP (see also Sections 1.1, 4.3.1 and 9.7). Opioid induced hyperalgesia (OIH) is a state of increased sensitivity to noxious stimuli occurring after exposure to high dose opioids (usually remifentanil). Patients exposed to high dose opioids in the perioperative period have higher postoperative pain scores and increased opioid use. OIH may result in spiralling opioid use (Fletcher 2014 **Level I**, 24 RCTs, n=1,494). Endogenous opioid analgesic systems are protective against the development of CPSP (Eippert 2009 **Level III-1 EH**; Yarnitsky 2008 **Level IV**, n=62). Prolonged opioid use leads to internalisation of mu opioid receptors at a cellular level. This may impair the functioning of the endogenous opioid analgesic system and increase sensitivity to pain leading to OIH and potentially CPSP (Glare 2019 **NR**).

1.4.4 | Predictive factors for chronic postsurgical pain

Risk evaluation for CPSP enables clinicians to address identified risk factors before surgery. This guides planning and discussion regarding expectations, the scope of planned surgery and possibility of changed approaches to the anaesthesia, pain management and even the procedure itself. Risk factors for CPSP have been identified in the preoperative, intraoperative and postoperative periods, and cover 6 broad domains: genetic, demographic, psychosocial, pain, clinical, and surgical factors (Schug 2017 **NR**).

Demographic factors such as younger age for adults and female gender influence the frequency of CPSP, as do psychological factors such as anxiety, depression, catastrophising, fear of surgery and hypervigilance (Theunissen 2012 **Level IV SR**, 29 studies, n=6,628; Hinrichs-Rocker 2009 **Level IV SR**, 50 studies, n≈25,000; Weinrib 2017 **NR**). Very young age may be a protective factor as hernia repair in children <3 mth of age did not lead to chronic pain in adulthood (Aasvang 2007 **Level IV**, n=651). In children aged 8–18 y, "*parent pain catastrophising*" was the main risk factor for the development of CPSP (Page 2013 **Level IV**, n-83). The significance of each risk factor varies with the operation but pre-existing psychological factors (high state anxiety and pain magnification as a component of catastrophising) increased the risk across two types of surgery (TKA and breast cancer surgery) (Masselin-Dubois 2013 **Level III-2**, n=189; Weinrib 2017 **NR**).

The intensity of acute postsurgical pain is a consistent predictor of CPSP (Chan 2011 **Level II**, n=640, JS 5; Althaus 2012 **Level IV**, n=150). This has been shown following a wide range of procedures including breast surgery (Bruce 2014 **Level IV**, n=362), thoracic surgery (Yarnitsky 2008 **Level IV**, n=62; Katz 1996 **Level IV**, n=30), gynaecological surgery (VanDenKerkhof 2012a **Level IV**, n=433), Caesarean section (Nikolajsen 2004 **Level IV**, n=220), lower limb amputation (Hanley 2007 **Level IV**, n=57), total hip arthroplasty (THA) (Nikolajsen 2006 **Level IV**, n=1,231) and inguinal herniotomy (Aasvang 2010a **Level IV**, n=464). After thoracic surgery, higher acute pain intensity postoperatively predicted the incidence of CPSP (OR 1.80; 95%CI 1.28 to 2.77), nearly doubling the chance of developing chronic pain for each point increase on a 10-point numerical rating scale (NRS) (Yarnitsky 2008 **Level IV**, n=62). Large scale observational studies have confirmed the

importance of acute pain in the development of CPSP with a 10% increase in the percentage of time in severe acute pain associated with a 30% increase in the incidence of CPSP at 12 mth (Fletcher 2015 **Level IV**, n=3,120). Sensitisation and "wind-up" of nociceptive pathways within the CNS is thought to play a significant role in the establishment and maintenance of chronic pain following an intense nociceptive stimulus. Nociceptive processes occurring in the periphery, including nerve injury, are also implicated in the transition from acute to chronic pain (Baron 2013 **NR**).

Preoperative chronic pain is a universal risk factor (Johansen 2014 **Level IV**, n=12,981; VanDenKerkhof 2012a **Level IV**, n=433; Wylde 2011 **Level IV**, n=1,294; Aasvang 2010a **Level IV**, n=464). This is likely due to the increase in sensitivity of the nociceptive system found in patients with chronic pain. This may partly explain the relatively high rates of CPSP following THA and TKA (25 and 44% respectively) (Wylde 2011 **Level IV**, n=1,294). Preoperative pain was the predictor that most commonly demonstrated a significant relationship with persistent pain following TKA across uni- and multivariate analyses. In a meta-analysis of univariate models, the largest effect sizes were found for preoperative pain at other sites, catastrophising and depression (Lewis 2015 **Level I**, 28 RCTs, n=29,993). For data from multivariate models catastrophising, preoperative pain, mental health and comorbidities had significant effects. Preoperative pain was also a risk factor for CPSP at 3 mth in trauma patients requiring orthopaedic surgery (OR: 1.17; 95% CI: 1.03, 1.32) (Edgley 2019 **Level III-2**, n=229).

Given the potential for opioids to interfere with endogenous analgesic systems, it is perhaps not surprising to find that preoperative opioid use increased the risk of CPSP after gynaecological surgery (RR 2.0; 95%CI 1.2 to 3.3) (VanDenKerkhof 2012a **Level IV**, n=433). In a prospective study of day case orthopaedic surgery, 8% developed CPSP if they were taking pre-operative analgesics with adequate analgesia (Hoofwijk 2015 **Level IV**, n=908). However, patients taking analgesics without relief had a much higher incidence of CPSP of 32%.

Presurgical sensitivity to painful stimuli, identified using some form of quantitative sensory testing (QST), variably accounts for 5–54% of the variance in acute postoperative pain and can predict risk for CPSP (Werner 2010 **Level I** [QUOROM], 15 RCTs, n=962). The relative efficacy of the endogenous descending inhibitory system determined by assessing DNIC partly predicted patients who developed CPSP after thoracotomy (OR 0.52; 95%CI 0.33 to 0.77) (Yarnitsky 2008 **Level IV**, n=62). Widespread pressure pain sensitivity was correlated with worse functional outcome following TKA (Wylde 2013 **Level III-3**, n=51). Sensitivity to noxious heat and mechanical stimuli did not correlate with CPSP in an unselected surgical population, whereas cold sensitivity correlated both with CPSP and comorbid chronic pain conditions (Johansen 2014 **Level IV**, n=12,981). Prior to herniotomy, high pain scores from a 47°C temperature probe were predictive of postherniotomy pain (OR 1.34; 95%CI 1.15 to 1.57) (Aasvang 2010a **Level IV**, n=464).

It is also likely that genetic and epigenetic factors influence both the sensitivity of individuals to analgesics and their risk of CPSP (Mauck 2014 **NR**; Buchheit 2012 **NR**). For example, different haplotypes of the gene for the enzyme catechol-O-methyltransferase (*COMT*), involved in the modulation of pain responses, were associated not only with differences in experimental pain sensitivity but also with the development of chronic temporomandibular joint disorder (TMD) (Nackley 2007 **Level IV**). In women undergoing hysterectomy the polymorphism rs4818 within the *COMT* gene was associated with the presence of CPSP at 3 mth but not 12 mth postoperatively (Hoofwijk 2019 **Level III-2**, n=345). However, opioid receptor mu-1 (*OPRM1*) genotype, but not *COMT* genotype, was associated with the development of CPSP after abdominal surgery (Kolesnikov 2013 **Level IV**, n=102). One prospective study of patients undergoing various surgical procedures did not reveal any correlation between 90 genetic markers and the incidence or severity of CPSP (Montes 2015 **Level IV**,

n=2,929). Overall, heritability estimates suggest that about 50% of the variability in CPSP rates is attributable to genetic variability. In order to apply these findings to individual patients, very large studies analysing tens of thousands of genetic samples will be needed to characterise patients at risk (Clarke 2015 **NR**) (see also Section 1.7).

To date, clinical risk factors remain the most reliable tools for the prediction of CPSP (Althaus 2012 **NR**). Attempts have been made to generate predictive models of CPSP but these do not yet have sufficient sensitivity and specificity to prove clinically useful. Using a training set of 150 patients with an incidence of CPSP of about 50%, five factors were independently predictive of developing CPSP, of which four can be assessed pre-operatively: pain in the surgical field, comorbid chronic pain at other sites, capacity overload and comorbid stress. Moderate to severe postoperative pain at POD 5 was the only significant postoperative factor. Patients with three to five risk factors were more likely to go on to develop CPSP than were those with zero to two factors (sensitivity 74%, specificity 65%).

Screening tools based on specific types of surgery have demonstrated better specificity, but identify many false positives. For example, for breast cancer surgery four factors were predictive of CPSP: preoperative pain at the site of surgery, high body mass index, axillary lymph node dissection and severity of acute pain on the 7th d after surgery (Meretoja 2017 **NR**). At the 20% risk level, the model had 32.8% and 47.4% sensitivity and 94.4% and 82.4% specificity in two cohorts from Denmark and Scotland, respectively. A predictive model for CPSP after inguinal hernia repair, hysterectomy or thoracotomy has been developed (Montes 2015 **Level IV**, n=2,929). The model included six clinical factors: surgical procedure, age, physical health, mental health, preoperative pain in the surgical field, and preoperative pain in another area. This model was a good fit (c-statistic 0.731; 95%CI 0.705 to 0.755). Interestingly, the same study found that 90 genetic markers did not predict CPSP.

The trajectory of daily pain scores after surgery has also been investigated as a predictor of CPSP (Chapman 2011 **Level IV**, n=502). Following TKA, 4 distinct acute pain trajectories were identified. Patients with a constantly high acute pain trajectory were at higher risk of CPSP (Page 2015 **Level IV**, n=173). Subacute pain after orthopaedic surgery at 10 d and 6 wk also predicted CPSP at 12 mth in one study (Andersson 2015 **Level IV**). Trajectories of anxiety and depression over time have also been assessed as a potential risk factor for CPSP, and patients with unremitting high levels of anxiety, but not depression were found to be more likely to experience CPSP following cardiac surgery (Page 2017 **Level IV**, n=173).

A summary of risk factors identified for the development of CPSP is presented in Table 1.3.

Table 1.3 | Risk factors for chronic postsurgical pain

Preoperative factors	Pain, moderate to severe, lasting >1 mth
	Repeat surgery
	Psychological vulnerability (eg catastrophising)
	Preoperative anxiety
	Female sex
	Younger age (adults)
	Workers' compensation
	Genetic predisposition
	Inefficient diffuse noxious inhibitory control
	Opioid use (particularly if ineffective)
Intraoperative factors	Surgical approach with risk of nerve damage
Postoperative factors	Pain (acute, moderate to severe and subacute)
	Radiation therapy to area
	Neurotoxic chemotherapy
	Depression
	Psychological vulnerability
	Neuroticism
	Anxiety
	Pain and anxiety trajectories

Sources: Adapted from Page 2017; Schug 2017; Johansen 2014; Wylde 2011; Hinrichs-Rocker 2009; Macrae 2008; Kehlet 2006.

1.4.5 | Mechanisms for the progression from acute to chronic pain

Central and peripheral sensitisation are the most likely underlying factors in the development of CPSP (Richebe 2018 **NR**; Lavand'homme 2017 **NR**). There is limited trial data to infer mechanisms and therefore most evidence relating to likely mechanisms is based on laboratory animal or epidemiological data (Peirs 2016 **NR BS**). Initiation of these processes is most likely in a situation where an individual is "primed" (eg by pre-existing pain) or susceptible (eg inefficient DNIC, psychological state or genetic predisposition) (Lavand'homme 2017 **NR**; Denk 2014 **NR**; Lavand'homme 2011 **NR**). The imposition of an intense surgical stimulus induces both central and peripheral changes (Baron 2013 **NR**). Maintenance of these intense nociceptive inputs by poorly controlled postoperative pain, peripheral nerve damage (D'Mello 2008 **NR**) and complications (eg wound infection) then lead on to a chronic pain state. It is proposed that these all lead to neuroplastic processes such as peripheral and central sensitisation. Such processes include inflammation at the site of tissue damage as well as ectopic discharges after nerve injury and lead to a barrage of afferent input that produces changes in the peripheral nerves, spinal cord, higher central pain pathways, somatosensory cortex and the sympathetic nervous system (see Section 1.1). Evidence for sensitisation includes the presence of larger area of secondary hyperalgesia at 48 h (88 vs 33 cm^2) in patients having iliac crest bone harvesting who developed CPSP with higher neuropathic pain scores on the Doleur Neuropathique 4 (DN4) questionnaire (4.3/10 vs 2.3) (Martinez 2012 **Level IV**). Similarly, following abdominal surgery, patients with analgesic regimens resulting in smaller areas of wound hyperalgesia (indicating less sensitisation) had a lower incidence of CPSP (Lavand'homme 2005 **Level II**, n=85, JS 5). Punctuate hyperalgesia

around a surgical incision could be shown in a large area, suggesting central sensitisation, which was suppressed by IV ketamine injection (Stubhaug 1997 **Level II**, n=20, JS 5).

The relative degree of ongoing inflammation or intraoperative nerve injury resulting in peripheral and central sensitisation may explain the variation in risk and, to an extent, the characteristics of CPSP for different operations (Simanski 2014 **Level IV**).

Psychological factors (depression, psychological vulnerability and stress) are important in the development of CPSP (Hinrichs-Rocker 2009 **Level IV SR**, 50 RCTs, n≈25,000) and cortical processing of nociceptive information and descending inhibitory and excitatory pathways provides a plausible mechanism for some of these effects. Functional connectivity and anatomical differences of corticolimbic structures involved in emotion and motivation predict chronic pain in some circumstances (Vachon-Presseau 2016 **Level IV EH**; Baliki 2012 **NR**).

1.4.6 | Prevention of chronic postsurgical pain

Effective prevention of CPSP is limited by an incomplete understanding of the mechanisms that generate it. However, some recognised risk factors are modifiable in the perioperative period. These include, body mass index, opioid use, preoperative pain and some psychological factors. In the postoperative period, attention to effective management of acute pain, limiting exposure to opioids and psychological support in rehabilitation and recovery of normal functioning are all likely to play a role.

Interventions evaluated thus far are divided into four broad groups and include regional and neuraxial analgesia, pharmacotherapy, surgery and multidisciplinary nonpharmacological interventions. Analgesic strategies for which the clinical efficacy outlasts the pharmacological activity are described as "preventive analgesia" (defined as analgesia that persists more than 5.5 half-lives of the medicine) and most likely rely on reducing peripheral and central sensitisation (Katz 2011 **NR**) (see also Section 1.5).

1.4.6.1 | Regional or neuraxial analgesia

Meta-analysis on the prevention of CPSP by regional anaesthesia found benefits for three procedure types: thoracotomy, breast cancer surgery and Caesarean section (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027). Following open thoracotomy (7 RCTs, n=499), epidural anaesthesia reduces the incidence of CPSP 3 to 18 mth following surgery compared to systemic analgesia (OR 0.52; 95%CI 0.32 to 0.84) (number-needed-to-treat [NNT] 7). For breast cancer surgery any form of regional anaesthesia (18 RCTs, n=1,297) reduces CPSP 3 to 12 mth after surgery compared with systemic analgesia (OR 0.43; 95%CI 0.28 to 0.68) (NNT 7); specifically paravertebral block (PVB) (6 RCTs, n=419) is effective (OR 0.61; 95%CI 0.39 to 0.97) (NNT 11). For Caesarean section (4 RCTs, n=551), a mixture of regional analgesia techniques, reduces CPSP from 3 to 8 mth (OR 0.46; 95%CI 0.28 to 0.78) (NNT 19). There is insufficient data to make clear recommendations regarding the timing of various local anaesthetic interventions (21 RCTs) and the impact on CPSP, but earlier administration of epidural prior to incision vs post amputation (4 RCTs, n=334) may provide benefit (Humble 2015 **Level I**, 32 RCTs, n=2,834).

For many procedures, studies investigating the effect of regional anaesthesia and analgesia on chronic pain outcomes are limited in number and have differing designs, which prevents meta-analysis due to high levels of heterogeneity. In patients undergoing open colonic resection, continuous perioperative epidural analgesia led to a lower risk of developing chronic pain up to 1 y after surgery compared with IV analgesia (Lavand'homme 2005 **Level II**, n=85, JS 5). In a case-control study, epidural anaesthesia reduced chronic pain at 6 mth after surgery (OR 0.19; 95%CI 0.05 to 0.76) (Bouman 2014 **Level III-2**). Spinal anaesthesia in comparison to general anaesthesia

reduced the risk of CPSP after Caesarean section (Nikolajsen 2004 **Level III-2**) and hysterectomy (OR 0.42; 95%CI 0.21 to 0.85) (Brandsborg 2007 **Level III-2**). The latter study found no difference in risk between abdominal and vaginal hysterectomy.

A systematic review on phantom limb pain prophylaxis showed that perioperative (pre, intra and postoperative) epidural analgesia reduced the incidence of severe phantom limb pain 12 mth after surgery (NNT 5.8) (Gehling 2003 **Level III-2 SR**, 9 studies, n=836). The use of epidural analgesia to prevent the development of phantom pain or CPSP following limb amputation may be a useful component of multimodal therapy in patients with severe preoperative pain (Karanikolas 2011 **Level II**, n=65, JS 5). See also Section 8.1.5.

The use of IV lidocaine for prevention of CPSP is discussed in Section 1.4.6.3 below.

1.4.6.2 | Local anaesthetic infiltration

Meta-analysis on the prevention of CPSP by local infiltration finds benefits for breast cancer surgery and iliac crest bone graft (ICBG) harvest (Weinstein 2018 **Level I** [Cochrane], 39 RCTs, n=3,027). For breast cancer surgery (6 RCTs, n=379), local anaesthetic infiltration reduces CPSP 3 to 12 mth after surgery vs systemic analgesia (OR 0.29; 95%CI 0.12 to 0.73) (NNT 7). For ICBG harvest (4 RCTs, n=159), continuous local anaesthetic infiltration reduces CPSP 3 to 12 mth after surgery vs systemic analgesia (OR 0.1; 95%CI 0.01 to 0.59) (NNT 3).

Local anaesthetic wound infiltration reduced the proportion of patients with chronic pain and neuropathic pain 2 mth following intracranial tumour resection (Batoz 2009 **Level II**, n=52, JS 3).

1.4.6.3 | Pharmacotherapy

Ketamine

Ketamine is commonly used to treat both acute and chronic pain. When used as a preventive analgesic, perioperative ketamine compared to placebo significantly reduces CPSP at 3 mth (5 RCTs, n unspecified) but only when administered for >24 h (OR 0.37; 95%CI 0.14 to 0.98) (Chaparro 2013 **Level I** [Cochrane], 14 RCTs [ketamine], n=1,388). At 6 mth (10 RCTs, n=516), perioperative ketamine reduces CPSP (OR 0.63; 95%CI 0.47 to 0.83), which remains significant when infused for <24 h (OR 0.45; 95%CI 0.26 to 0.78). These effects were predominantly in abdominal surgery. Another meta-analysis found a benefit of perioperative IV ketamine vs placebo in reducing the incidence of CPSP at 3 mth (RR 0.74; 95%CI 0.60 to 0.93) (NNT 12), 6 mth (RR 0.70; 95%CI 0.50 to 0.98) (NNT 14) but not at 12 mth postoperatively (McNicol 2014 **Level I**, 14 RCTs [IV route], n=1,586) (11 RCTs overlap); such beneficial effects were not found with epidural administration of ketamine (3 RCTs, n=302).

A network meta-analysis investigating multiple pharmacological interventions to reduce CPSP identified ketamine as the highest ranked in terms of efficacy and safety (Ning 2018 **Level I** [NMA], 24 RCTs, n unspecified). In thoracic surgery, low dose ketamine infusion (0.1 mg/kg/hr) reduced opioid use for 24 h and pain at 48 h, but did not affect CPSP at 3, 6 or 12 mth (Chumbley 2019 **Level II**, n=70, JS 5).

Opioids

High dose intra-operative opioids, particularly remifentanil, have been shown to result in opioid induced hyperalgesia, increased pain and 24 h opioid use in the postoperative period which may be associated with CPSP (Fletcher 2014 **Level I**, 27 RCTs, n=1,494). The intra-operative use of remifentanil in cardiac surgery also resulted in a higher incidence of CPSP at 1 y (OR 8.9; 95%CI 1.6 to 49.0) (van Gulik 2012 **Level III-2**, n=90).

Alpha-2-delta ligands (gabapentinoids)

Two previous parallel meta-analyses (10 RCT overlap) and a correction of one of these investigated the use of perioperative gabapentin or pregabalin in reducing CPSP across a diverse range of procedures (Chaparro 2013 **Level I** [Cochrane], 15 RCTs [gabapentin and pregabalin], n=1,300; Clarke 2012 **Level I** [PRISMA], 11 RCTs, n=930; Clarke 2013 **Level I**, 5 RCTs, n=875). The overall conclusion was that there was limited or no benefit in the setting of significant heterogeneity.

In addressing the issue of potential bias due to unpublished data, a meta-analysis of pregabalin and CPSP included 79% unpublished trials (Martinez 2017 **Level I** [PRISMA], 18 RCTs, n=2,485). There was no benefit with pregabalin use in the prevention of CPSP overall at 3, 6 or 12 mth postoperatively, in cardiac, visceral or orthopaedic surgery (OR 0.87 [at 3 mth]; 95%CI 0.66 to 1.14). There was, however, a reduction in chronic postsurgical neuropathic pain in four published trials (4 RCT, n=451) (OR 0.16; 95%CI 0.04 to 0.73). These results reflect weak evidence due to the small size of most included studies, the variability in existing study design, doses used, duration of treatment and measured outcomes, and positive publication bias.

IV lidocaine (lignocaine)

IV lidocaine has preventive effects on acute postoperative pain (Barreveld 2013 **Level I**, 16 RCTs [lidocaine], n=847) (see Section 1.5) and reduces CPSP following breast cancer surgery at 3 mth compared to systemic analgesics alone (OR 0.24; 95%CI 0.08 to 0.69) (Weinstein 2018 **Level I** [Cochrane], 2 RCTs, n=97 [IV lidocaine]) (1 RCT overlap). A meta-analysis of IV lidocaine versus placebo in the prevention of CPSP at 3 mth across a range of surgeries (predominantly mastectomy), identified a significant benefit (OR 0.29; 95%CI 0.18 to 0.48) (NNT 5), although numbers were too small to specifically identify safety concerns (Bailey 2018 **Level I**, 6 RCTs, n=420) (2 RCT overlap with Weinstein 2018).

Others

Following mastectomy, 10 d treatment with venlafaxine (37.5 mg/d) commencing preoperatively was associated with significantly lower burning and stabbing pain after 6 mth (Amr 2010 **Level II**, n=150, JS 3).

Planned subgroup analysis of the intraoperative use of nitrous oxide (ENIGMA-2) revealed that this intervention prevents CPSP in Chinese patients and those with variants in the methylene tetrahydrofolate reductase gene (RR 0.70; 95%CI 0.50 to 0.98) suggesting that there may be a genetic component to vulnerability to CPSP (Chan 2016 **Level II**, n=674, JS 5); there was no benefit in non-Chinese patients overall.

1.4.6.3 | Modification of surgical approach

Minimally invasive and laparoscopic surgery has made a significant impact on the severity of acute postsurgical pain but has resulted in little impact on the prevalence of CPSP (Aasvang 2010a **Level III-2**, n=464). While VATS vs open thoracic surgery reduced the risk of post-thoracotomy pain (aOR 0.33; 95%CI 0.13 to 0.86) and neuropathic pain (aOR 0.18; 95%CI 0.04-0.85), it still carries a significant risk (35% incidence) (Shanthanna 2016 **Level III-3**, n=106); this is confirmed in another study (VATS 13.3% vs thoracotomy 32.2%) (Wang 2017 **Level III-2**, n=298).

Deliberate neurectomy (of the ilioinguinal nerve) for inguinal hernia repair reduced the incidence of CPSP (from 21 to 6%) in one RCT (Malekpour 2008 **Level II**, n=100, JS 4) and in another study (Smeds 2010 **Level III-2**), while an earlier nonrandomised multicentre prospective study found this approach increased CPSP risk (Alfieri 2006 **Level III-2**, n=973). Intraoperative nerve identification of the iliohypogastric, ilioinguinal and genitofemoral nerves did not reduce the risk of development of sensory loss or postherniotomy pain syndrome compared with nonidentification (Bischoff 2012 **Level III-3**, n=244). International

guidelines for the reduction in CPSP following inguinal herniorrhaphy have been developed, recommending preservation of all three nerves (Alfieri 2011 **GL**).

Sparing of the intercostobrachial nerve during mastectomy with axillary dissection reduces the likelihood of a patient having hyposensitivity but not hypersensitivity (Warrier 2014 **Level I** [PRISMA], 3 RCTs, n=309). Cryoanalgesia of the intercostal (IC) nerves at the time of thoracotomy results in an increase in chronic pain in comparison to IV PCA or epidural analgesia or in conjunction with epidural analgesia (Humble 2015 **Level I**, 6 RCTs [cryoanalgesia], n=186).

1.4.6.4 | Multidisciplinary approaches

The impact of psychological interventions delivered in the perioperative period to prevent CPSP has been assessed by a systematic review (Wang 2018 **Level I** [PRISMA], 15 RCTs, n=2,220). Perioperative education has no effect on CPSP, while perioperative cognitive-behavioural therapy and/or relaxation training reduce the severity of CPSP based on evidence of moderate quality (MD -1.06/10; 95%CI -1.56 to -0.55). Preemptive and preventive pain psychoeducation decrease the length of stay and improve quality of acute postsurgical pain relief (Horn 2020 **Level I** [PRISMA], 43 RCTs, n unspecified). The authors concluded that preemptive pain psychoeducation would result in a decreased incidence of CPSP given that severe acute postsurgical pain and catastrophising were both significant risk factors.

Transitional pain services
New models of acute pain services have been suggested to manage pain and opioid use in the perioperative period. The '*Transitional Pain Service*' aims to optimise pain and opioid use prior to surgery, devise individualised intraoperative opioid sparing analgesic plans and manage pain postoperatively beyond the time of discharge from hospital (Katz 2015 **NR**). This approach is intended to reduce CPSP and inappropriate long-term opioid use. Psychological strategies including Acceptance and Commitment Therapy (ACT) are employed to assist in rehabilitating patients and treat or prevent CPSP (Huang 2016 **NR**). A similar model of '*Acute Pain Service Outpatient Clinic*' has been established in Finland (Tiippana 2016 **Level III-3**). Of the first 200 high risk patients referred to the clinic, 70% had evidence of neuropathic CPSP. The median time to referral to the clinic from surgery was 2 mth and patients were followed up for a median of 2.8 mth. At discharge from hospital, half the patients were using weak opioids, one third strong opioids and 70% were taking gabapentinoids. At discharge from the clinic, use of these drugs was approximately halved. One fifth of the patients were referred to the chronic pain clinic for ongoing management.

See also the following Section 1.5 for more examples of the use of preemptive and preventive analgesic interventions in attempts to reduce the risk of chronic pain after surgery and Sections 8.1.5 to 8.1.6 for more details on prevention of phantom pain after limb amputation and other postoperative pain syndromes.

KEY MESSAGES

1. Perioperative IV ketamine reduces the incidence of chronic postsurgical pain in selected procedures (**S**) (**Level I** [Cochrane Review]).

2. Following thoracotomy, epidural analgesia reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).

3. Following breast cancer surgery, paravertebral block (**S**), local infiltration (**N**) (**Level I** [Cochrane Review]) and IV lidocaine reduce the incidence of chronic postsurgical pain (**N**) (**Level I** [PRISMA]).

4. For iliac crest bone graft harvest, continuous local anaesthetic infiltration reduces the incidence of chronic postsurgical pain (**N**) (**Level I** [Cochrane Review])

5. Pregabalin reduces the incidence of chronic postsurgical neuropathic pain, but does not affect non-neuropathic chronic postsurgical pain (**N**) (**Level I** [PRISMA]).

6. Sparing of the intercostobrachial nerve during mastectomy does not decrease chest wall hypersensitivity (**U**) (**Level I** [PRISMA]).

7. Cryoanalgesia of the intercostal nerves at the time of thoracotomy results in no improvement in acute pain but an increase in chronic pain (**U**) (**Level I**).

8. There is significant association between anxiety, pain catastrophising (**U**) (**Level III-2 SR**), depression, psychological vulnerability and stress (**U**) (**Level IV SR**) and the subsequent development of chronic postsurgical pain.

9. Other risk factors that predispose to the development of chronic postsurgical pain include the severity of presurgical chronic pain and postsurgical acute pain and intraoperative nerve injury (**U**) (**Level IV SR**).

10. Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Caesarean section (**U**) (**Level III-2**).

11. Chronic postsurgical pain is common and may lead to significant disability (**S**) (**Level IV**).

12. Chronic postsurgical pain often has a neuropathic component (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Gabapentin has no demonstrated effect in preventing chronic postsurgical pain; considerable uncertainty exists regarding efficacy with contradictory meta-analyses of a few, usually small, studies with a large degree of heterogeneity (**Q**).

☑ Implementation of transitional pain services may help manage the complex issues of prolonged postoperative opioid use and chronic postsurgical pain (**N**).

1.5 | Pre-emptive and preventive analgesia

The terms 'pre-emptive' and 'preventive' analgesia have a highly specific meaning with respect to pain neurophysiology and sensitisation. The understanding of pre-emptive analgesia has evolved since the term was first coined in early 1988 (Wall 1988 **NR**). In laboratory studies, administration of an analgesic prior to an acute nociceptive stimulus more effectively minimised dorsal horn changes associated with central sensitisation than the same analgesic given after the pain state was established (see Section 1.1) (Woolf 1983 **BS**). This led to the hypothesis that pain relief prior to surgery may enhance postoperative pain management when compared with the same analgesia administered during or following surgery; that is, "pre-emptive preoperative analgesia" (Wall 1988 **NR**). 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 (Rosero 2014a **NR**; Katz 2002 **NR;** Kissin 1994 **NR**).

Central and peripheral sensitisation affects both the intensity of acute pain and the persistence of pain well into the postoperative period and beyond (see also Section 1.4). This is complex and relates not only to the skin incision but also to the extent of intraoperative tissue and nerve injury, postoperative inflammation and the nervous system's response. The research focus has shifted from the "timing" of a single analgesic intervention to the concept of modifying sensitisation and thus having a longer-term impact on pain relief. This is termed "preventive" analgesia (Kissin 1994 **NR**) rather than pre-emptive analgesia. The differences between these two terms relate to the timing and outcomes being described, because both aim to minimise sensitisation. "Pre-emptive" analgesia, as described above, relates to the timing of administration of the analgesic intervention prior to the insult and is measured in terms of pain intensity or related outcomes. "Preventive" analgesia is the persistence of analgesic treatment efficacy beyond its expected duration of effect (see Table 1.4). This had been defined as analgesia that persists for >5.5 half-lives of a medicine, to ensure complete washout of any direct pharmacological effect (Katz 2011 **NR**). A useful summary of medicines and their criterion value of 5.5 half-lives has been published (Katz 2008b **NR**). In clinical practice, preventive analgesia appears to be the most relevant and, of pharmacological options, holds the most hope for minimising chronic pain after surgery or trauma because it decreases central sensitisation and "wind-up". An important consideration to maximise the benefit of any analgesic strategy is that the active intervention should be continued for as long as the sensitising stimulus persists (ie well into the postoperative period) (Pogatzki-Zahn 2006 **NR**; Dahl 2004 **NR**). However, from a "preventive" perspective, the critical aspect is that the effect of the intervention is sufficient to modify sensitisation and hence longer-term outcomes; the timing and duration for specific interventions still require clarification.

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 during surgery. The key clarification point is the timing of administration "pre" insult/surgery. A treatment given pre-emptively can also be preventive if it satisfies the below definition.

Preventive analgesia	Postoperative pain and/or analgesic consumption is reduced relative to another treatment, a placebo treatment or no treatment with the effect observed at a point in time beyond the expected duration of action of the intervention (eg 5.5 half-lives of the medicine). The intervention may or may not be initiated before surgery.

Sources: Moiniche 2002; Katz 2002; Katz 2011; Rosero 2014b

1.5.1 | Pre-emptive analgesia

The benefits of pre-emptive analgesia have been questioned (Katz 2008b **Level I**, 27 RCTs, n unspecified; Moiniche 2002 **Level I**, 80 RCTs, n=3,761; Dahl 2004 **NR**). However, one meta-analysis provided support for pre-emptive analgesia (Ong 2005 **Level I**, 66 RCTs, n=3,261). 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 is most marked for epidural analgesia, with improvements found in all outcomes (13 RCTs, n=653) (overall effect size 0.38; 95%CI 0.28 to 0.47). Pre-emptive effects of local anaesthetic wound infiltration and NSAID administration were also suggested but reanalysis is required as one of the positive studies for each of these treatments has subsequently been withdrawn (White 2011 **NR**). As a result of this withdrawal, evidence supporting the pre-emptive effects of nonselective NSAIDS (nsNSAIDs) and COX-2 inhibitors is equivocal (White 2009 **NR**). Reductions in analgesic consumption ranged from 44–58%, which the authors regarded as clinically significant, but associated changes in adverse effects were not analysed. Pain score results were equivocal for systemic NMDA antagonists (effect size [ES] 0.00; 95%CI -0.19 to 0.20) (7 RCTs, n=418) and there was no clear evidence for a pre-emptive effect of opioids (ES -0.24; 95%CI -0.46 to -0.01) (7 RCTs, n=324).

Following thoracotomy, pre-emptive thoracic epidural analgesia (local anaesthetic opioid prior to surgery) reduces the severity of acute pain on coughing for up to 48 h, with a marginal effect on pain at rest compared with the same therapy initiated postoperatively (Bong 2005 **Level I**, 6 RCTs, n=458). Acute pain intensity was a predictor of chronic pain at 6 mth in two studies but there was no statistically significant difference in the incidence of chronic pain between the pre-emptive epidural (39.6%) vs control epidural (48.6%) groups. Pre-emptive analgesia with epidural use in thoracotomy identified lower postoperative pain scores, reduced pro-inflammatory biomarkers and shortened hospital LOS (Yang 2015 **Level II**, n=90, JS 3).

In single-stage TKA, pre-emptive epidural analgesia was associated with lower postoperative pain scores, fewer days with pain following surgery (mean ± SD 64.3 d ± 21.3 vs 142.4 d ± 80.0) and less CPSP at 3 mth (24 vs 56.5%) (Rao 2020 **Level II**, n=50, JS 3); there were no differences in morphine consumption or LOS.

A Cochrane review investigated opioids commenced prior to incision compared to those commenced following incision; this review uses the term "preventive" to indicate the continued use of opioids into the postoperative period and so its findings are actually more in line with the above definition of "pre-emptive" (Doleman 2018 **Level I** [Cochrane], 20 RCTs, n=1,343). There were no differences in 6 h or 24 to 48 h pain score outcomes, but a small reduction was found in 24 h morphine consumption in the pre-incision group (MD -4.9 mg; 95%CI -9.4 to -0.4).

Across a range of procedures, IV paracetamol given before incision is more effective than post incision in reducing pain at 1 h (MD -0.50/10; 95%CI -0.98 to -0.02) and 2 h (MD -0.34/10; 95%CI - 0.67 to -0.01), 24 h opioid consumption (SMD 0.52; 95%CI -0.98 to -0.06) and

postoperative vomiting (RR 0.50; 95%CI 0.31 to 0.83) (Doleman 2015 **Level I** [PRISMA], 7 RCTs, n=544). IV paracetamol reduces PONV when administered before recovery from anaesthesia (Apfel 2013 **Level I** [PRISMA], 30 RCTs, n=2,364). This effect is correlated to pain relief achieved but not to reduced opioid consumption.

In total abdominal hysterectomy, gabapentin given only prior to surgery compared to gabapentin given pre- and postoperatively found both interventions decreased 24 h morphine requirements compared to placebo (preoperatively only SMD -0.69; 95%CI -1.20 to-0.07; pre and postoperatively -1.45; 95% CI -1.79 to -1.11) (Alayed 2014 **Level I SR**, 14 RCTs, n=891); the effect of gabapentin in reducing morphine consumption was stronger in the preoperative only group than in the preoperative and postoperative group. The design of the studies in this meta-analysis did not allow for evaluation of a true pre-emptive effect because all active treatments were given preoperatively.

Dexketoprofen administered 30 min pre- vs 10 min post-incision in patients having abdominal hysterectomy resulted in lower pain scores for up to 4 h postoperatively and reduced morphine consumption for up to 24 h (Gelir 2016 **Level II**, n=50, JS 3); all patients received intraoperative ketamine infusions and there was no difference in time to first analgesic request.

A combination of paracetamol, ketoprofen and pregabalin administered 4 h pre-surgery vs control, with all drugs being then given to both groups post-incision for at least 48 h, resulted in improved pain scores for up to 48 h and reduced PCA opioid requirements (Raja 2019 **Level II**, n=97, JS 4).

The reason for there being a limited number of valid clinical studies investigating 'pre-emptive' analgesia is that investigators often fail to compare the same technique pre- and post-incision or they apply the intervention after sensitisation has occurred eg in trauma or injury. The variability in clinical trial design coupled with the complexity of clinical pain management means that, with the exception of epidural analgesia, benefits remain unclear regarding pre-emptive analgesia in a clinical setting.

1.5.2 | Preventive analgesia

A true preventive analgesic effect needs to be assessed many days or even months after the analgesic intervention has ceased. A large number of studies published use the term 'preventive' where the investigation often simply compares the addition of a preoperative dose of an analgesic to a preoperative placebo (possibly continuing the medications postoperatively) with analgesic outcomes assessed for a relatively short period – this is not 'preventive' in the neurophysiological sense and such studies are not discussed here.

A systematic review analysed dichotomous trial outcomes (overall positive or negative outcomes) (Katz 2008b **Level I**, 39 RCTs, n unspecified) and identified overall beneficial acute preventive effects following the use of a range of different medicines (28 positive RCTs, 11 negative RCTs). Again, results of this meta-analysis might be affected by the subsequent withdrawal of some of the studies included (White 2011 **NR**). The methodology was unable to identify specific therapeutic techniques that may be of benefit.

The use of local anaesthetics (neuraxial, perineural or systemic) demonstrates a preventive analgesic effect in the perioperative period whether given pre- or postincision (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027; Barreveld 2013 **Level I**, 89 RCTs, n unspecified). Meta-analysis on the prevention of CPSP by regional anaesthesia found benefits for three procedure types: thoracotomy, breast cancer surgery and Caesarean section (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027). IV lidocaine versus placebo provides a significant benefit in prevention of CPSP at 3 mth across a range of surgeries (Bailey 2018 **Level I**, 6 RCTs, n=420) (2 RCTs overlap with Weinstein 2018 **Level I** [Cochrane]) 2 RCTs, n=97 [IV lidocaine]) (see Section 1.4 for details).

Activation of the NMDA receptor plays an important role in central sensitisation and many studies have focussed on the ability of NMDA-receptor antagonists to produce pre-emptive or preventive analgesic effects. A medicine which, when used perioperatively, reduces CPSP has by definition a preventive analgesic effect (see Section 1.4). The preventive effects of perioperative ketamine, dextromethorphan and magnesium on CPSP are described in Sections 1.4 and 4.6. Analgesic benefit is seen in the acute postoperative period with ketamine following a range of doses, timings and procedures (Laskowski 2011 **Level I** [PRISMA], 70 RCTS, n=4,701) supported by a network meta-analysis investigating multiple pharmacological interventions to reduce CPSP which identified ketamine as the highest ranked in terms of efficacy and safety (Ning 2018 **Level I** [NMA], 24 RCTs, n unspecified) (see also Section 4.6.1). However, in the immediate postoperative period, it is difficult to separate persistence of direct pharmacological effects from preventive actions, as many studies continued treatment for over 24 h. Expanding potential indications for ketamine in depression have led to exploration of its potential 'metaplastic' effects on synaptic transmission whereby a brief exposure may result in persisting changes in neuronal long term potentiation (Izumi 2014 **BS**); this may explain in part its effect in CPSP.

The alpha-2-delta ligands, gabapentin and pregabalin, reduce opioid requirements and improve analgesia when given perioperatively (see Section 4.8). However, even though some of these studies used only single-dose therapy, the range of doses, duration of follow-up and long half-life of gabapentin (6 to 7 h) means that an early preventive benefit is difficult to discern from a direct pharmacological effect. Longer term preventive effects on CPSP are discussed in Sections 1.4 and 4.8.

In a study of multimodal epidural 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 y after surgery was demonstrated with continuous perioperative epidural analgesia (Lavand'homme 2005 **Level II**, n=85, JS 5). Residual pain at 1 y was lowest in patients who received intraoperative vs postoperative epidural analgesia. Epidural analgesia commenced pre-incision versus post-incision for TKA resulted in less CPSP at 3 mth (24 vs 56.5%) (Rao 2020 **Level II**, n=50, JS 3) indicating a possible preventive effect (see Section 1.5.1 above for other details).

Epidural calcitonin, bupivacaine and fentanyl versus epidural bupivacaine and fentanyl alone reduced phantom pain, allodynia and hyperalgesia at 6 and 12 mth following proximal or distal amputation in the lower limb (Yousef 2017 **Level II**, n=60, JS 3).

KEY MESSAGES

Pre-emptive analgesia
1. The timing of opioid administration (preincision rather than postincision) may reduce further opioid consumption over 24 h, but has no effect on pain scores **(N)** (**Level I** [Cochrane Review])

2. Pre-emptive use of paracetamol across a range of procedures reduces pain scores up to 2 h, opioid consumption for up to 24 h and postoperative nausea and vomiting (**N**) (**Level I** [PRISMA]).

3. Pre-emptive epidural analgesia has a significant effect on postoperative pain relief (**S**) (**Level I**).

Preventive analgesia
4. Epidural, regional and systemic local anaesthetic administration shows preventive analgesic effects in reducing chronic postsurgical pain (**S**) (**Level I** [Cochrane Review])

5. NMDA-receptor antagonists (ketamine) reduce the incidence of chronic postsurgical pain in selected procedures (**S**) (**Level I** [Cochrane Review]).

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

☑ In clinical trials assessing acute postoperative pain for many systemic medicines, the range of doses administered, the variable durations of follow-up and variable half-lives following infusion or repeated dosing means that "early" preventive effects, although possible, are difficult to discern from persistence of direct pharmacological effects (**U**).

1.6 | Adverse physiological and psychological effects of acute pain

1.6.1 | Acute pain and the injury response

Acute pain, and its associated injury and treatment, triggers a complex haemodynamic, metabolic, neurohumoral, immune as well as somatosensory response (see Figure 1.2). Clinically, acute pain is commonly associated with actual tissue damage. This tissue damage may be due to trauma or surgery. The complete physiological response to the insult has a quantifiable molecular and cellular response. Importantly, this response is generated in a range of anatomical compartments. These include rapid adaptations at the site of injury, along ascending neuronal projections, within the spinal cord, at higher brain centres and within distal organs. These disparate events are triggered by a coordinated array of neuronal, autocrine and paracrine signalling events. Many of these events do not result in nociceptive outcomes but may detrimentally impact an individual's injury recovery or increase risk of secondary complications. Importantly, all of these events can occur in a conscious individual whose prior life experience may prime or protect them from the molecular consequences and perception-processing of a painful response.

Figure 1.2 | The injury response

Triggers and predisposing factors	Mediators	Injury response
Surgical trauma or injury	Neural	Pain experience, primary and secondary hyperalgesia (peripheral and central sensitisation)

Preoperative pain	Immune factors
	Proteins and other molecules:
	  growth factors
	  eicosanoids
	  nitric oxide
	  others
		Inflammation
		Haemodynamic

Psychological factors	Endocrine	Catabolism
Social and environmental factors	Metabolic	Physical deconditioning
Genetic factors		Psychological effects
Anaesthesia and analgesia, other medications		Other adaptations systemic

Source: Modified from NHMRC 1999.

It is difficult to separate the complex array of potential individual or interacting triggers associated with pain from other aspects of the broader physiological response observed clinically (see Figure 1.2). However, some data have been obtained with experimental pain in the absence of injury. For example, electrical stimulation of the abdominal wall results in a painful experience

(intensity 8/10) and an associated hormonal/metabolic response, which includes increased levels of cortisol, catecholamines and glucagon, and a decrease in insulin sensitivity (Greisen 2001 **Level II EH**). A systematic review of the effect of experimental pain on the autonomic nervous system, assessed by heart rate variability, determined that experimental pain increases baroreflex activity and decreases parasympathetic activity (Koenig 2014 **Level IV EH SR**, 20 studies, n unspecified). Factors such as time of day, possibly owing to nociceptive control by diurnally active hormones, contribute to reported differences in thermal pain (both cold and heat) (Aviram 2015 **Level II EH**, n=48, JS 3). Some of these environmental conditioning factors may change the perception rather than the nociceptive signal itself eg sleep deprivation in healthy controls causes hyperalgesia which may be caused by a reduction in cortical cognitive or perceptual mechanisms, rather than sensory nociceptive amplification (Odegard 2015 **Level II EH**, n=33, JS 4).

Although acute pain is only one of the important triggers of the "injury response" (see Figure 1.2), as the magnitude and duration of the response is related to the magnitude and duration of the nociceptive stimulus, effective pharmacological pain relief may have a significant impact on this response (Moselli 2011 **Level II**, n=35, JS 3), although this may be variable (Fant 2013 **Level II**, n=26, JS 3; Liu 2008 **NR**; Carli 2008 **NR**). Beyond pharmacological interventions, mere distraction of attention away from the pain protects against experimental pain-induced changes in heart rate variability (Koenig 2014 **Level IV EH SR**, 20 studies, n unspecified). Importantly, negative expectations in patients created by verbal suggestions can lead to the "nocebo" response, defined as experiencing greater pain to the same nociceptive stimulus (Petersen 2014 **Level III-1 EH SR** [PRISMA], 10 studies, n=344).

As noted above, the release of systemic factors such as proinflammatory cytokines as a result of pain and trauma associated with surgery or injury may contribute to multiple physiological responses that hamper the recovery of a patient. Limiting these effects by analgesic techniques may affect some surgical outcomes. A group of patients having abdominal surgery were randomised to receive intraoperative epidural analgesia or IV opioid analgesia, with both groups receiving postoperative epidural analgesia (Moselli 2011 **Level II**, n=35, JS 3). In the intraoperative epidural group, inflammatory markers were lower up to 24 h postoperatively and minor complications were reduced in number (39 vs 76%), although there was no difference in major complications or LOS. Postoperative ileus is attenuated in patients receiving IV lidocaine infusions compared to saline in patients undergoing colonic surgery (Sun 2012 **Level I** [PRISMA], 21 RCTs, n=1,108; Vigneault 2011 **Level I** [PRISMA], 29 RCTs, n=1,754) (15 RCT overlap). Analgesic and bowel motility benefits of lidocaine were more marked when administered via the thoracic epidural route than by IV infusion (Kuo 2006 **Level II**, n=60, JS 5); however, both lidocaine groups were associated with reduced opioid consumption compared with saline. The postoperative decreases in proinflammatory cytokines, such as interleukin (IL)-6, IL-8 and IL-1RA (a competitive inhibitor of IL-1β), were associated with more rapid return of bowel function following abdominal surgery. Ketamine, administered intraoperatively, is associated with reduced IL-6 levels post operatively, suggesting an anti-inflammatory effect in addition to analgesic benefits (Dale 2012 **Level I** [PRISMA], 6 RCTs, n=331).

In addition to the stress responses to surgery and analgesia, aberrant neuronal firing during acute pain creates a state of altered cell function in nociceptive pathways. This may not be perceived as pain by higher brain centres (eg under general anaesthesia) nor acknowledged consciously by the individual. Cellular adaptations to acute nociceptive inputs in primary and secondary fibres are well established to drive peripheral and central sensitisation (Baron 2013 **NR**; von Hehn 2012 **NR**; Woolf 2011 **NR**; Kuner 2010 **NR**). Critically, these result in multiple changes to gene transcription and protein translation (see also Section 1.1).

1.6.2 | Adverse physiological effects

Clinically significant injury responses that are often associated with nociceptive stimuli trigger diffuse physiological responses such as stress and inflammation, which leads to hyperalgesia, hyperglycaemia, protein catabolism, increased free fatty acid levels (lipolysis) and changes in water and electrolyte flux (Carli 2008 **NR**; Liu 2008 **NR**) (see Table 1.5). In addition, increased sympathetic activity has diverse effects on the cardiovascular, gastrointestinal and respiratory systems and on coagulation, endocrine, immune and psychological function (Prabhakar 2014 **NR**; Cardinale 2011 **NR**; Blackburn 2011 **NR**).

Table 1.5 | Metabolic immunological and endocrine responses to injury

Endocrine	Catabolic hormones	ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagons,
	Anabolic hormones	Insulin, testosterone
Immune	Mitochondrial initiation	Alarmins (DAMP molecules)
	Proinflammatory followed by compensatory response	IL-1, TNFα, IL-6, IL4, IL8, IL10 Chemokines
Metabolic *Carbohydrate*	Hyperglycaemia, glucose intolerance, insulin resistance	Glycogenolysis, gluconeogenesis (cortisol, glucagon, growth hormone, adrenaline, free fatty acids) Insulin secretion/activation
Protein	Muscle protein catabolism, synthesis of acute phase proteins	Cortisol, adrenaline, glucagon, IL-1, IL-6, TNF
Lipid	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; DAMP: damage-associated molecular pattern; ECF: extracellular fluid; ICF: intracellular fluid; IL: interleukin; TNF: tumour necrosis factor.*

Source: *Modified from NHMRC 1999.*

1.6.3 | Pain and analgesia: effects on injury-induced organ dysfunction

Pain from injury activates a range of adverse physiological effects (Prabhakar 2014 **NR**; Cardinale 2011 **NR**; Blackburn 2011 **NR**). Increased sympathetic efferent nerve activity increases heart rate, contractility 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 motility and contribute to ileus. Perioperative neurocognitive disorders such as postoperative delirium are exacerbated by under-treated pain and associated factors such as

stress and inflammation. In patients with fractured neck of femur, delirium was associated with lack of analgesic use (Thompson 2018 **Level IV**, n=688). In elderly patients, postoperative delirium is decreased with the use of multi-component interventions, which include effective analgesia (Siddiqi 2016 **Level I** [Cochrane], 39 RCTs, n=16,082).

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 (Lord 2014 **NR**). Alterations to glucose metabolism and accelerated protein breakdown also contribute to the injury response. These factors need to be considered when evaluating analgesic interventions. 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 2008 **NR**). Analgesic technique may reduce adverse physiological impact and improve surgical outcomes. Often a multimodal approach to anaesthesia, pain management, the surgical stress response and perioperative care is undertaken, making it difficult to separate individual factors involved in outcome; especially with multifaceted strategies such as with enhanced recovery after surgery (ERAS) protocols (Kehlet 2018 **NR**). The influence of epidural anaesthesia and analgesia on outcome has been evaluated (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044) (see also Section 5.6).

There is also limited evidence that stress and opioid analgesia in some circumstances may inhibit immune function, promoting tumour growth or metastasis. Regional anaesthetic and opioid-sparing analgesic techniques might have a beneficial effect on rates of cancer recurrence after tumour resection but overall study results are still unclear (Meserve 2014 **NR**; Colvin 2012 **NR**).

KEY MESSAGES

1. Recognition of the importance of postoperative rehabilitation including pharmacological, physical, psychological and nutritional components has led to enhanced recovery (**U**) (**Level I** [PRISMA]).

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**).

1.6.4 | Adverse psychological effects

Psychological changes associated with acute pain have received less clinical attention than those associated with chronic pain, however they have been well-studied in experimental contexts, especially regarding interference with attention and cognitive processes such as learning and memory. Clinically, sustained acute nociceptive input, as often occurs after surgery, trauma or burns, can also have a major influence on psychological function, which may in turn increase the risk of progression to chronic pain (Glare 2019 **NR**). In addition, pre-operative psychological characteristics, in concert with other factors (eg genetic factors and pre-operative pain), have

also been found predictive of adverse reactions to postoperative pain (Yang 2019 **Level III-2 SR**, 33 studies, n=53,362; Lindberg 2017 **Level IV**, n=188; Schug 2017 **NR**).

Failure to relieve acute pain may result in increasing anxiety, inability to sleep, demoralisation, a feeling of helplessness, loss of control, and an inability to think and interact with others; in the most extreme situations, where patients can no longer communicate, effectively they have lost their autonomy (VanDenKerkhof 2012b **Level IV**, n=76; Cousins 2004 **NR**). In turn, these psychological responses in the acute phase may be major determinants of progression to chronic pain conditions, such as chronic postsurgical pain (CPSP), typically in combination with other known risk factors (Jenewein 2009 **Level III-2**, n=90; Williamson 2009 **Level III-2**, n=1,290; Schug 2017 **NR**; Young Casey 2008 **NR**). In breast cancer surgery patients, anxiety and low psychological robustness (positive affect and dispositional optimism) emerged as significant predictors of acute pain with distress being the strongest predictor of chronic pain (McCowat 2019 **Level IV SR**, 12 studies, n=3,452). However, the relationship between depression and CPSP was uncertain

In acute pain, attention has also focussed on perioperative neurocognitive disorders (PND), including delirium and the research outcome of postoperative cognitive dysfunction (POCD). Both pain itself and analgesic drugs can exacerbate PND, especially delirium (Scottish Intercollegiate Guidelines Network 2019 **GL**). Although the aetiology of PND (and POCD) is unclear, factors include dysregulation of cerebral neurotransmitters, patient factors (age, preoperative cognitive function), and perioperative pharmacological therapy (Evered 2018 **NR**). Neurotransmitters involved in PND include acetylcholine and serotonin, especially in the elderly (Inouye 2014 **NR**); hence analgesics and adjuvants with anticholinergic or sedative effects should be avoided where possible in at-risk patients (Scottish Intercollegiate Guidelines Network 2019 **GL**; American Geriatrics Society 2015 **GL**). Effective non-opioid-based acute pain management in older patients helps reduce delirium (Scottish Intercollegiate Guidelines Network 2019 **GL**; Mahanna-Gabrielli 2019 **NR**) (see also Sections 1.2, 1.4, 9.2).

KEY MESSAGES

1. Postoperative delirium is exacerbated by unrelieved acute pain and by overuse of sedating analgesics, in particular opioids (**N**) (**Level IV**).

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

☑ Failure to relieve acute pain can lead to psychological distress (**N**).

1.7 | Genetics and acute pain

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

Pharmacogenomics deals with the influence of variations in the human genome on response (both beneficial and undesirable) to medicines in patients. By correlating gene alterations with a medicine's efficacy or toxicity, it is possible to gain a better understanding of the causes of interpatient variability in response to a specific medicine and so to develop a rational means to optimise pharmacological 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, ion channels, enzymes) contribute to the large interpatient variability in postoperative opioid requirements (De Gregori 2016 **NR**; Trescot 2014 **NR**). Information from genotyping may help in selecting the analgesic medicine and the dosing regimen for an individual patient (Packiasabapathy 2018 **NR**; Allegri 2010 **NR**; Lotsch 2006 **NR**). Nevertheless, given the complexity of pain pathways, in very few cases is a single gene variant contributing substantially to response variability, but rather there are a large number of small contributions from multiple genes.

Although there is increasing information from studies, often small numbers of subjects are involved and therefore translation into clinical practice is still limited (Trescot 2014 **NR**; Stamer 2007b **NR**). Nevertheless, some preliminary estimates for dose adaptations are possible (Allegri 2010 **NR**; Lotsch 2006 **NR**). Importantly however, genetic factors must be considered within the context of the multiple interacting physiological, psychological, age-related, cultural, ethnic and environmental factors that influence individual responses to pain and analgesia (Sadhasivam 2014 **NR**; Searle 2009a **NR**; Kim 2009 **NR**).

1.7.1 | Single gene pain disorders

A number of rare pain-related conditions have been identified through family linkage mapping, which are due to single gene mutations (Mendelian gene).

Recognised hereditary syndromes associated with reduced pain sensation include the following.

- Channelopathy-associated insensitivity to pain (CAIP) is 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$1.7 is located in peripheral (dorsal root and sympathetic ganglion) neurones and plays an important role in action potential generation in these cells. Mutations that result in loss of Na$_v$1.7 function cause affected individuals to be unable to feel physical pain (Bennett 2014 **NR**). Patients with a single-nucleotide polymorphism (SNP) in *SCN9A* (3312T; 5.5% frequency) had lower postoperative pain sensitivity after pancreatectomy, lower PCA requirements and a lower likelihood of developing inadequate analgesia than those carrying the 3312G allele (OR 0.10; 95%CI 0.01 to 0.76) (Duan 2013 **Level III-2**, n=200).
- 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 (NTRK1 gene) (Vetter 2017 **NR**; Auer-Grumbach 2013 **NR**; Mogil 2012 **NR**). These syndromes present as various combinations of loss or reduced sensitivity to pain accompanied by other autonomic and sensory deficits. HSAN type IV is also known as congenital insensitivity to pain with anhydrosis (CIPA).

Recognised hereditary syndromes associated with increased pain sensation include (Mogil 2012 **NR**):

- Erythromelalgia and paroxysmal extreme pain disorder, also known as familial rectal disorder, both of which are due to different gain-of-function mutations of sodium channel Nav1.7 (SCN9A) (Dabby 2012 **NR**);
- Familial hemiplegic migraine;
- Hereditary neuralgic amyotrophy; and
- Hereditary pancreatitis (Rebours 2012 **NR**).

1.7.2 | Genetic influences on sensitivity to pain

Apart from these rare Mendelian inherited conditions, "pain sensitivity" variability is thought to vary up to 50% in the general population due to genetic differences, with environmental influences responsible for the remainder of variability (Norbury 2007 **Level IV**, n=196). Twin studies have helped identify inheritable traits for development of back pain, postherpetic neuralgia, fibromyalgia and other common painful conditions (Mogil 2012 **NR**).

While several hundred genes have been identified as associated with pain expression in mice, they are not necessarily relevant to humans (LaCroix-Fralish 2011 **SR BS**) and have been studied in chronic and not acute pain (Kringel 2018 **Level IV**; Zorina-Lichtenwalter 2016 **NR**). Evidence for a genetic association with more common pain conditions has come from association studies, which require large cohorts (Mogil 2012 **NR**). Studies often suffer from low sample sizes and the restricted number of potential genotype variants studied. Many findings of an association of a particular gene allele with pain sensitivity have not been replicated in subsequent studies, so caution is needed in this area.

Many genetic variants have been associated with pain sensitivity (Crist 2014 **NR**); the most commonly studied genes include:

- Mu opioid receptor (*OPRM1*);
- Catechol-O-methyltransferase (*COMT*);
- Guanosine triphosphate cyclohydrolase 1;
- Transient receptor potential (*TRPV1*); and
- Melanocortin-1 receptor (*MC1R*)

Other gene variants that have been associated with alterations in pain sensitivity in acute pain states include *ADRB2, HTR2A, IL1RN, KCNJ6, MAOA* and *MAOB* (Mogil 2012 **NR), P2RX7** (Kambur 2018 **Level III-2**, n=3,847) and *TAOK3* (Cook-Sather 2014 **Level III-2**, n=617). Often studies have addressed postoperative analgesic requirements as the index of pain sensitivity rather than use of experimental pain models.

1.7.2.1 | OPRM1

A variant of the gene encoding the mu opioid receptor *OPRM1,* A118G SNP, was targeted as a very promising candidate for modulation of analgesia and has been the most studied variant (Crist 2014 **NR**).

Overall findings on the effects of this SNP remain contradictory (Crist 2014 **NR**). In a random-effects meta-analysis in the postoperative setting, *OPRM1* 118G-allele carriers have higher mean opioid requirements than *OPRM1* 118AA homozygotes (SMD -0.18; p=0.003) (Hwang 2014 **Level III-2 SR**, 18 studies, n=4,607). These findings were robust in a subgroup analysis of Asian patients, whose frequency of the G variant is about 40% compared to about 15% for Caucasians (SMD -0.21; p=0.001), morphine users (SMD -0.29; p<0.001) and patients after bowel surgery (SMD -0.20; p=0.008). A preceding systematic review found a similar but smaller effect (SMD 0.096;

95%CI 0.025 to 0.167) of *OPRM1* 118G with increased opioid requirements in the perioperative and postoperative period (Walter 2013 **Level III-2 SR**, 14 studies, n=3,346); there was no significant association of *OPRM1* 118G with opioid requirements, when using the random-effects environment (Cohen's d 0.044; 95%CI -0.113 to 0.202). A positive finding was obtained in 1,000 women undergoing breast cancer surgery in which the GG cohort required about 33% more oxycodone than the AA cohort (Cajanus 2014 **Level III-2 SR**, n=1,000). For epidural analgesia using fentanyl during labour however, G-allele (AG+GG) carriers of the *OPRM1* 118 polymorphism required lower (not higher) fentanyl doses to achieve adequate pain relief compared to those with the AA homozygote (SMD -0.24; 95%CI -0.44 to -0.03) (Song 2013 **Level III-2 SR**, 6 studies, n=838). *OPRM1* 304A/G polymorphism did not influence the duration of effect or the requirement for breakthrough analgesia after intrathecal (IT) opioid administration for labour pain (Wong 2010 **Level III-2**, n=293). There was also no effect of A118G mu-opioid receptor polymorphism on duration of analgesia found in a subsequent study, but patients of Hispanic/African origin had increased duration of analgesia and pruritus vs Jewish/Arabic patients in labour (Ginosar 2013 **Level III-2**, n=125).

    OPRM1 A118G seems to modulate effects of opioids given in experimental pain; in the clinical setting it has limited impact with no clinical relevance in Caucasians, but explains increased opioid requirements in Asians. Studies that assessed different haplotypes of the *OPRM1* and combinations of genetic variants, eg *OPRM1*, COMT and ESR1, found greater predictability suggesting more complexity (De Gregori 2016 **Level III-2**, n=201; Reyes-Gibby 2007 **Level III-2**, n=207; Mura 2013 **NR**). Overall *OPRM1* 118 polymorphisms may be too complex to be used as a predictive tool for individual opioid dosing (Mogil 2012 **NR**).

1.7.2.2 | COMT

COMT metabolises noradrenaline, adrenaline, and dopamine and has been implicated in the modulation of pain. COMT inhibition or low activity via genetic polymorphisms may lead to increased pain sensitivity via beta-adrenergic receptor-dependent mechanisms (Nackley 2007 **NR**). Haplotypes with high COMT activity are associated with low pain sensitivity to mechanical and thermal stimuli (Diatchenko 2005 **NR**). The Val158Met polymorphism influences the activity of the COMT enzyme with the Met158 allele associated with low COMT activity and increased pain sensitivity (Vuilleumier 2012 **NR**), leading to greater morphine requirements post-surgery in adults (Dai 2010 **Level IV**, n=69) and children (Sadhasivam 2014 **Level IV**, n=149).

    A large study undertaken to address influence of *COMT* polymorphism on postoperative pain in a homogenous ethnic sample of 1,000 women having breast surgery showed no association with any *COMT* polymorphism and postoperative oxycodone requirements (Kambur 2013 **Level III-2**, n=1,000). Furthermore, the most studied *COMT* mutation, Val158Met, showed no association with pain levels in these patients, but two previously unstudied mutations did. In contrast, in 152 patients undergoing nephrectomy, the 31 patients with Val/Val genotype consumed more IV morphine than 61 Met/Met patients (36%; 95%CI 31 to 41) (Candiotti 2014 **Level III-2**, n=152). Combinations of several genetic mutations act together to determine pain sensitivity associated with COMT (Smith 2014 **Level III-2**, n=398). Similarly, genetic association studies using COMT variants have also revealed conflicting results (Belfer 2011 **NR**).

1.7.2.3 | TRPA1

Emerging evidence suggests that epigenetic variations of the TRPA1 receptor may be responsible for some of the genetically determined individual differences in pain sensitivity (Gombert 2017 **Level III-2 EH**, n=75; Bell 2014 **Level III-2 EH**, n=100).

There is considerable complexity associated with genetic mutations influencing pain sensitivity and much to be unravelled before clear evidenced-based conclusions can be drawn.

1.7.3 | Drug metabolism

Drug-metabolising enzymes represent a major target for identifying associations between an individual's genetic profile and drug response (pharmacogenetics) (Trescot 2014 **NR**; Stamer 2007c **NR**). The polymorphic cytochrome P450 enzymes metabolise most medicines and show interindividual variability in their catalytic activity. There are 57 enzymes in this family of which 9 are clinically relevant to drug metabolism: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/3A5, all of which have different and often overlapping activity. Medicines can be substrates, inhibitors or inducers of metabolism of analgesic medications.

CYP2D6, CYP2C19, and CYP2C9 are highly polymorphic and are involved in approximately 40% of CYP-mediated drug metabolism. Of these, CYP2D6 is the most relevant to analgesic medications. Those who have the genetic variants resulting in poor metabolism by CYP2D6 are likely to have more severe postoperative pain than those who have other variants (Yang 2012 **Level III-2**, n=236).

CYP2D6 gene influences the metabolism of many medications including codeine, tramadol, oxycodone, hydrocodone, dextromethorphan, amitriptyline, nortriptyline, duloxetine, metoclopramide and venlafaxine. Specifically, CYP2D6 metabolises codeine, dihydrocodeine, hydrocodone, oxycodone and tramadol to their more potent hydroxyl metabolites, which have a higher affinity for the mu receptor (Somogyi 2007 **NR**). For additional detail related to individual opioids see Section 4.3.1.

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 normal metabolisers; intermediate metabolisers are heterozygotes with one reduced function and one nonfunctional allele; poor metabolisers have no functionally active alleles and have minimal or no enzyme activity (Crews 2014 **NR**; Vuilleumier 2012 **NR**; Zhou 2009a **NR**; Zhou 2009b **NR**). Ultrarapid metabolisers have multiple copies of the wildtype *CYP2D6* alleles (Crews 2014 **NR**; Vuilleumier 2012 **NR**; Stamer 2007b **NR**).

There are large interethnic differences in the frequencies of the variant alleles. For example, in Caucasian populations, 8–10% of people are poor metabolisers and 1-3% are ultrarapid metabolisers (Crews 2014 **NR**; Vuilleumier 2012 **NR**; Stamer 2007b **NR**). The proportion of ultrarapid metabolisers is higher (up to 29%) in Middle Eastern and Northern African populations and lower (0.5%) in Asian populations (Stamer 2007c **NR**). The proportion of poor metabolisers is lower in Asian and African American populations (Zhou 2017 **Level IV SR**, 5 population-scale sequencing projects, n=56,945; Yee 2013 **Level IV**, n=75; Holmquist 2009 **NR**).

Other genetic factors indirectly affecting the metabolism or effect of analgesics are liver cell transporter proteins: organic cation transporter (OCT1) (Fukuda 2013 **Level III-2**, n=146); ABCC3 (Venkatasubramanian 2014 **Level III-2**, n=220) and ATP-binding cassette subfamily member B1 (also known as multidrug resistance protein [MDR]1 or p-glycoprotein) (Sadhasivam 2015 **Level III-2**, n=263). The latter affects efflux transport of morphine at the blood-brain barrier and thereby cerebral pharmacokinetics.

Further considerations are the differential risk with genetic differences and varying prevalence of racial/ethnic phenotypes (Anderson 2014 **NR**) and consequent variability in sensitivity to efficacy and adverse effects (Jimenez 2012 **Level III-3**, n=68; Fukuda 2013 **Level IV**, n=146; Palada 2018 **NR**).

1.7.3.1 | Codeine and CYP2D6

In children and adults receiving codeine for postoperative pain, very low or undetectable plasma morphine levels have been noted in those with poor metaboliser or intermediate metaboliser genotypes, but with variable impact on analgesia (Williams 2002 **Level II**, n=96, JS 3; Poulsen 1998 **Level IV**, n=81; Persson 1995 **Level IV**, n=11).

CYP2D6 genotypes predicting ultrarapid metabolism resulted in about 50% higher plasma morphine and its glucuronides concentrations following oral codeine compared with the extensive metaboliser (Kirchheiner 2007 **Level IV**). Both the impaired renal clearance of these metabolites and genetic background (CYP2D6 ultrarapid metaboliser status) have been implicated in reports of respiratory depression due to codeine in adults and children (Friedrichsdorf 2013 **Level IV**; Kelly 2012 **Level IV**; Stamer 2007b **Level IV**). (See also Sections 4.3.1.3 and 10.4.4.5)

1.7.3.2 | Tramadol and CYP2D6

O-demethylation of tramadol by the enzyme CYP2D6 produces the active metabolite (+)-O-demethyltramadol (M1), which has an affinity for mu-opioid receptors that is approximately 200 times higher than the parent drug (Lai 1996 **BS**). Poor metabolisers have significantly lower plasma concentrations of M1 compared with both homozygous and heterozygous extensive metabolisers (Fliegert 2005 **Level II**, n=26, JS 2; Kirchheiner 2008 **Level III-2**, n=22; Stamer 2003 **Level III-3**, n=300) and experience less analgesia (Stamer 2007a **Level III-3**, n=174; Stamer 2003 **Level III-3**, n=300). As with codeine, impaired renal clearance of metabolites and genetic background (CYP2D6 ultrarapid metaboliser status) have been implicated in cases of respiratory depression after tramadol (Desmeules 1996 **Level II**, n=10, JS 3**;** Stamer 2008 **CR**) (see also Section 4.3.1.3).

1.7.3.3 | Methadone

Genetic polymorphisms in genes coding for methadone-metabolising enzymes, transporter proteins (p-glycoprotein) and mu-opioid receptors may explain part of the observed interindividual variation in the pharmacokinetics and pharmacodynamics of methadone; blood concentrations may vary up to 20-fold for a given dose (Somogyi 2014 **NR**; Li 2008 **NR**).

Methadone is metabolised primarily by CYP2B6 and to a minor extent by CYP3A4 (Kharasch 2017 **NR**; Kapur 2011 **NR**). Differing effects for isomers of methadone have also been reported; genetic variability in CYP2B6 influenced (S)-methadone (less active isomer) and, to a lesser extent, (R)-methadone (more active isomer) plasma concentrations (Somogyi 2014 **NR**). In addition, genetic polymorphisms in *CYP2C19* gene (responsible for a minor role in methadone metabolism) have effects on methadone-maintenance dosing, (R)-methadone/methadone ratio and cardiotoxicity of methadone (prolonged QT interval) (Wang 2013 **NR**) (see also Section 4.3.1.5).

1.7.3.4 | Oxycodone

Oxycodone is metabolised primarily to noroxycodone by CYP3A4 (≈80%) and by CYP2D6 to oxymorphone (Lalovic 2006 **Level IV EH**). The O-demethylated metabolite oxymorphone has up to 40-fold higher affinity for the mu receptor and eight-fold higher potency than oxycodone and represents about 11% of its overall metabolism (Crews 2014 **NR**). Oxymorphone may contribute significantly to the overall analgesic effect of oxycodone in experimental pain (Samer 2010 **EH**); noroxycodone, the major metabolite, is only a weak mu-receptor agonist (Lalovic 2006 **EH**; Coluzzi 2005 **NR**).

The dependence of oxymorphone concentrations on CYP2D6 activity and its high potency explains why oxycodone's pharmacodynamics and pharmacokinetics are dependent on *CYP2D6* polymorphism (Soderberg Lofdal 2013 **NR**), at least in experimental pain (Samer 2010 **EH**).

However, in acute postoperative pain, *CYP2D6* genotype had either no influence on oxycodone requirements (Zwisler 2010 **Level III-2**, n=270) or a small difference in dosage that was not gene-dose related (Stamer 2013 **Level III-2**, n=121). Overall, the data on the association of *CYP2D6* pheno/genotype and oxycodone response in acute pain are unconvincing (Huddart 2018 **NR**) (see also Section 4.3.1.2).

1.7.3.5 | NSAIDs

Wide variability in gene expression and functional polymorphisms in the COX-2 gene (*PTGS2*) may explain part of the interindividual variations in acute pain and the analgesic efficacy of nsNSAIDs and coxibs; this may be useful to predict patient risk and benefit from medicines based on individual genetic variations (Somogyi 2007 **NR**; Lee 2006 **Level III-2**).

NSAIDs such as ibuprofen, diclofenac and celecoxib are metabolised by CYP2C9 (Rollason 2014 **NR**). Between 1 and 3% of Caucasians are poor metabolisers. Homozygous carriers of the *CYP2C9*3* allele may accumulate celecoxib and ibuprofen in blood and tissues and be at risk of increased adverse effects (Kirchheiner 2003 **Level III-3**, n=26; Kirchheiner 2002 **Level IV**; Rollason 2014 **NR**; Stamer 2007b **NR**), but this is unlikely to affect acute pain response.

KEY MESSAGES

1. CYP2D6 polymorphisms affect plasma concentrations of active metabolites of codeine, oxycodone and tramadol with variable effects on analgesic efficacy (**U**) (**Level II**).

2. The mu opioid receptor OPRM1 polymorphism is unlikely to be clinically relevant as a single gene mutation in Caucasian populations and is more likely to be of clinical relevance in Asian populations (**U**) (**Level III-2 SR**).

3. CYP2D6 ultrarapid metabolisers are at increased risk of codeine and tramadol toxicity (**U**) (**Level IV**).

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

☑ Genetic polymorphisms contribute to the wide interindividual variability in plasma concentrations of a given dose of methadone (**U**).

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