PAIN PHARMACOLOGY AND ANALGESIA

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Contents

Summary

Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. Pain may be described according to severity (mild, moderate, severe), duration (acute or chronic) or type (nociceptive, inflammatory, neuropathic). In the last two decades, considerable research directed at enhancing our collective understanding of the neurobiology of pain has revealed that persistent ongoing pain secondary to tissue inflammation or peripheral nerve injury is underpinned by considerable complexity and plasticity in the pain signaling system. Following tissue or peripheral nerve injury, there is sensitization of the somatosensory system so that innocuous stimuli are detected as painful (allodynia) or there is a heightened response to painful stimuli (hyperalgesia).

Although a large number of “pain” targets for potential modulation by small molecules or biologics have been identified with several of these molecules now in preclinical or clinical development, these potential new pain medicines are yet to reach the clinic. Hence, pain is currently managed according to the World Health Organisation’s 3-step Analgesic Ladder. For mild pain, non-opioid analgesics such as paracetamol (acetaminophen) and nonsteroidal anti-inflammatory drugs are recommended, with adjuvants (e.g. antidepressants, anticonvulsants or anti-arrhythmics) added as required if

pain has a neuropathic component. For moderate pain, weak opioids such as codeine and tramadol are added to non-opioids and/or adjuvants, as required. For moderate to severe pain, strong opioids are recommended with morphine as the drug of choice due to its ready availability worldwide at low cost. Strong opioids may be co-administered with non-opioids and with adjuvants, as required. In the next decade, a new generation of pain medicines is likely to reach the market, thereby expanding the armamentarium of drugs available to clinicians for the management of persistent on-going pain.

1. Pain Definitions

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey and Bogduk, 1994). Individuals may describe their pain in terms of its severity, duration and type. As a patient's emotional response to a painful stimulus contributes significantly to the pain experience, there are often large inter-individual differences in reports of pain severity evoked by apparently similar stimuli. Hence, there are no objective measures that can be used with validity to compare the severity of one person's pain with that of another. Instead, a number of pain rating scales have been devised and validated for quantifying changes in pain severity within individuals (Melzack and Katz, 2006).

1.1 Pain – According to Duration

1.1.1 Acute Pain

The IASP has defined acute pain as "pain of recent onset and probable limited duration; it usually has an identifiable temporal and causal relationship to injury or disease" (Merskey and Bogduk, 1994). Acute pain such as that which occurs following surgery, trauma, burns or myocardial infarction, may be regarded as an adaptive response with a physiologically important role. Acute pain generally comprises two phases. The first phase (lasting seconds) "alerts" the individual to potentially dangerous stimuli and the second, subchronic phase (lasting hours to days) may be regarded as a "protective" mechanism characterized by "guarding" of the injured tissue as a means of promoting healing and recovery (Merskey and Bogduk, 1994).

1.1.2 Chronic Pain

Chronic pain is defined as "pain lasting for long periods of time. It commonly persists beyond the time of healing of an injury and frequently there may not be any clearly identifiable cause" (Merskey and Bogduk, 1994). Persistent pain is often regarded as a maladaptive response that confers no physiological advantage, such that the pain state itself has become the "disease", requiring treatment (Cousins, 2007). Persistent pain may have multiple components including nociceptive pain, inflammatory pain and neuropathic pain, which are variously defined as follows (Devor and Seltzer, 1999):

1.2 Pain – According to Type

1.2.1 Nociceptive Pain

Nociceptive pain refers to the normal, acute pain sensation evoked by activation of

specialized primary afferent nerve fibres (nociceptors) located in undamaged or previously undamaged skin, viscera and other organs in the absence of sensitization.

1.2.2 Inflammatory Pain

Inflammatory pain such as arthritis may be defined as hypersensitivity that arises in inflamed tissue following sensitization of peripheral nerve terminals.

1.2.3 Neuropathic Pain

Neuropathic pain is defined by the IASP as pain due to a dysfunction of, or damage to, a nerve or group of nerves, primarily peripheral nerves, although pain due to central nervous system (CNS) damage ("central pain") may share these characteristics. Examples of peripheral neuropathic pain are painful diabetic neuropathy, post-herpetic neuralgia (post-shingles pain), HIV-AIDS (human immunodeficiency virus-acquired immunodeficiency syndrome) neuropathy and chemotherapy-induced neuropathic pain. The most common types of central neuropathic pain are post-stroke pain, pain in multiple sclerosis and spinal cord injury pain.

At present, persistent inflammatory and neuropathic pains present great challenges to general practitioners and pain specialists alike, because the currently available drugs used to treat these conditions have significant limitations. Moreover, opioids that are effective for the relief of moderate to severe nociceptive pain are often considerably less effective for the relief of neuropathic pain, particularly when administered by systemic routes.

1.3 Emotional Response to Pain

Although the IASP definition of pain recognizes its multi-dimensional nature, incorporating a patient's emotional response to a noxious stimulus, it is only relatively recently that brain imaging techniques have begun to explore this latter aspect in humans, and most research attention has focused on brain imaging of acute pain (Kupers and Kehlet, 2006). By contrast, in the last two decades, there have been considerable advances in our collective understanding of the neurobiology of pain, particularly persistent pain, which has revealed many novel potentially "druggable" targets for the development of new pain therapeutics for human use (Pace et al., 2006; Schaible, 2007). Hence, this chapter has been structured in two parts, with the first providing an overview of the pain signaling system, highlighting recent advances in our understanding of the neurobiology of pain with emphasis on potential targets for the development of new pain therapeutics. The second provides an overview of medications currently used for managing acute and chronic pain.

2. Pain Signaling System

2.1 Pain Detection

Put simply, pain signals from peripheral tissue exposed to damaging or potentially damaging stimuli are detected by nociceptors located in the affected tissue and whose

cell bodies are located in the dorsal root ganglia (Sherrington, 1906). Nociceptive (pain) signals are transmitted via nociceptive primary afferent nerve fibres (so-called first-order neurones) to the outer layers (laminae I and II) of the dorsal aspect of the spinal cord (dorsal horn) (Sherrington, 1906). Nociceptive signals are then relayed from the dorsal horn by second-order neurones via spinothalamic tracts to higher centres in the brain, which may in turn activate descending inhibitory mechanisms to reduce the severity of the perceived pain to tolerable levels (Figure 1) (Sherrington, 1906; Dubner, 2004; Yaksh, 2006).

2.2 Functional Characteristics of the Pain Signaling Apparatus

2.2.1 Nociceptors

Nociceptors (Figure 1) in the skin (cutaneous), muscle, joints, viscera and dura that detect noxious (damaging or potentially damaging) stimuli (Sherrington, 1906), respond in aggregate to a broad range of physical (heat, cold, pressure) or chemical (acid, irritants, inflammatory mediators) stimuli, but only at intensities capable of causing tissue damage (Millan, 1999; Caterina et al., 2000). Nociceptive information is relayed from the nociceptors to the CNS via axons that are either small (2-6 μm) myelinated Aδ-fibres with a conduction velocity in the range 4-30 m/s, or thin (0.4-1.2 μm), unmyelinated C-fibres with conduction velocities < 2.5 m/s. Additionally, cutaneous mechanoreceptors are often supplied by large (> 10 μm), fast (30-100 m/s) myelinated Aβ fibres that, in the absence of tissue or nerve injury, are responsive only to touch, vibration, pressure and other modes of non-noxious, low intensity mechanical stimuli (Woolf et al., 1994; Millan, 1999; Willis and Coggeshall, 2004). Generally, a single discharge of an individual nociceptor is not perceived as noxious and many nociceptors need to be recruited for "pain" to be perceived (Millan, 1999; Willis and Coggeshall, 2004). However, in the presence of persistent inflammation or nerve injury, Aβ fibres undergo phenotypic change such that non-noxious stimuli may become encoded as noxious stimuli (Dubner, 2004).

2.2.2 Primary Sensory Neurones

The cell bodies of primary afferent sensory neurons that innervate the limbs and trunk are located in sensory ganglia associated with spinal nerves (dorsal root ganglia). The axons of these primary afferent sensory neurones give rise to a peripheral branch that innervates various tissue types and a central branch that travels through a dorsal root to enter the spinal cord and synapse with second-order neurones (Todd and Koerber, 2006). Fibres that innervate skin are referred to as cutaneous sensory neurons, whereas afferent fibres inervating abdominal or pelvic viscera are termed visceral afferents (Todd and Koerber, 2006). Together, these primary sensory neurones are a means for providing ongoing surveillance of the external environment as well as the ongoing state of the body itself (Todd and Koerber, 2006).

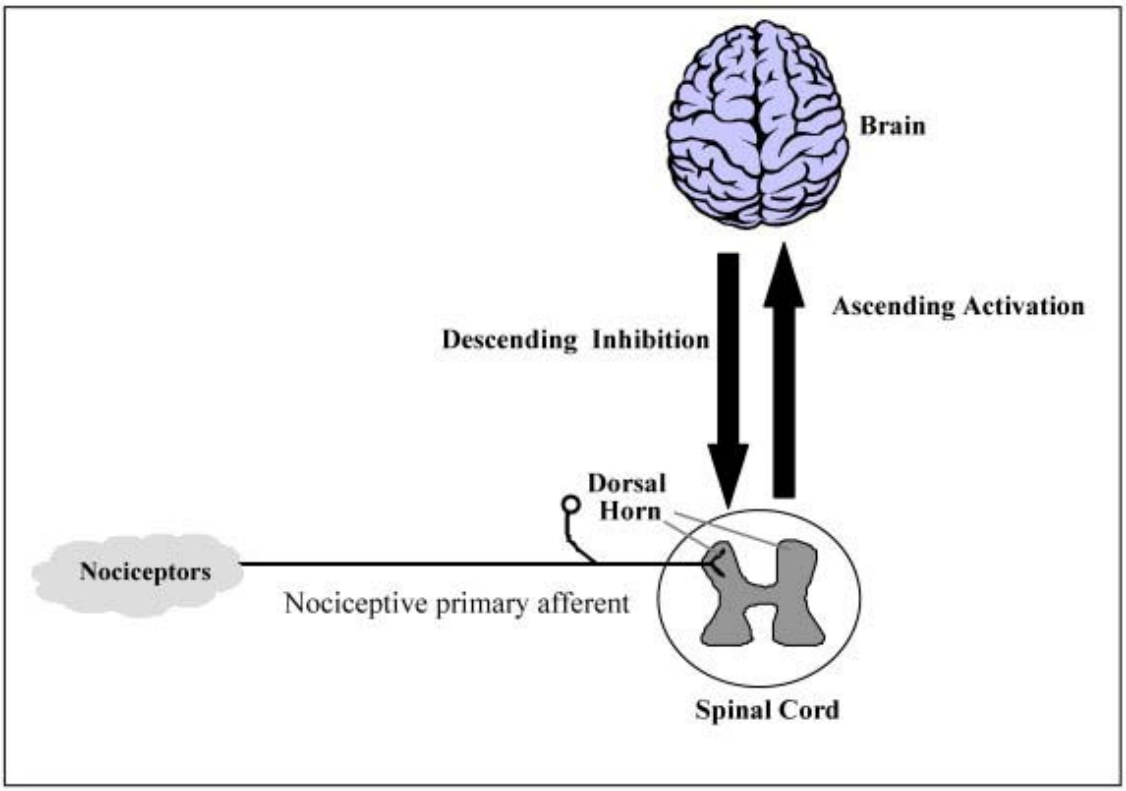

Figure 1. Nociceptive signals are detected by specialized primary afferent nerve fibres (nociceptors) located in the injured peripheral tissue from where they are transmitted to the dorsal horn of the spinal cord. Nociceptive signals are then relayed to higher centres in the brain, which may result in activation of the descending inhibitory system to reduce the severity of the perceived pain. (See also Figure 6)

2.2.3 Primary Sensory Neurons and the Spinal Cord

The central terminals of nociceptive primary afferents mainly terminate in the superficial layers (laminae I and II) of the dorsal horn, the site of the first synapse in ascending pathways that convey sensory information to the brain (Todd and Koerber, 2006). However, it should be noted that myelinated and unmyelinated fibres that signal the presence of innocuous mechanical and thermal stimuli also project to these same laminae (Todd and Koerber, 2006). Low-threshold Aβ mechanoreceptors terminate in deeper laminae (Willis and Coggeshall, 2004). The rostrocaudal and mediolateral location of the central terminals of primary afferents in the dorsal horn encodes the location of the afferents' peripheral receptive field, generating a somatotopic map of the body surface in the horizontal plane of the dorsal horn (Woolf and Salter, 2006). At the level of individual nerve territories, the map is organized such that neighbouring peripheral fields occupy contiguous parts of the spinal cord (Woolf and Salter, 2006).

2.2.4 Spinal Cord Neurons

Dorsal horn neurones can be classified as (i) projection neurons, (ii) local interneurons, or (iii) propriospinal neurons (Willis and Coggeshall, 2004). Although projection neurons are the primary output from the spinal cord, transfering sensory information

from the spinal cord to the brain, they represent a small minority of the total number of cells in the dorsal horn (Woolf and Salter, 2006).

2.2.4.1 Projection Neurons and the Spinal Cord

Neurons with axons that project to the brain are present in relatively large numbers in lamina I and are scattered through the deeper part of the dorsal horn (laminae III-VI) and the ventral horn. Those in lamina I and many of those from deeper laminae have axons that cross the midline and ascend to a variety of supraspinal targets including the thalamus, midbrain periaqueductal grey matter, lateral parabrachial area of the pons and various parts of the medullary reticular formation (Todd and Koerber, 2006). Projection neurons are also involved in the activation of descending control systems, which in turn modulate dorsal horn neurons through both excitatory and inhibitory mechanisms (Woolf and Salter, 2006).

2.2.4.2 Spinal Interneurons

The majority of the dorsal horn neuronal population is comprised of interneurons that arborize in the same segment generally close to the cell body, although it is also quite common for cells to give rise to axons that extend into other laminae (Todd and Koerber, 2006; Woolf and Salter, 2006). Dorsal horn inter-neurones may be inhibitory cells that use gamma-amino-butyric acid (GABA) and/or glycine as their principal neurotransmitter, and excitatory glutamatergic cells (Todd and Spike, 1993). GABAergic cells comprise ~25-30% of neurones in lamina 1/II and ~40% of those in lamina III (Todd and Sullivan, 1990). Many inhibitory interneurons are spontaneously active, and in this way maintain an ongoing tonic inhibitory control over dorsal horn nociceptive processing (Woolf and Salter, 2006). Excitatory glutamatergic interneurons identified by the presence of vesicular glutamate transporters (VGLUTs), are present in large numbers of axons in the spinal cord (Todd et al., 2003). Within the dorsal horn, VGLUT1-expressing neurons are largely restricted to the deeper laminae (III-VI) with VGLUT present mainly on the central terminals of myelinated primary afferents (Todd et al., 2003) whereas VGLUT2 is present on numerous axon terminals that are more evenly distributed throughout the dorsal horn (Todd et al., 2003).

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Davis M.P. (2005) Buprenorphine in cancer pain. *Support Care Cancer* **13**, 878-887. [Review of the clinical pharmacology of buprenorphine and various formulations including a recently developed polymer patch formulation.]

De Biasi S., Rustioni A. (1988) Glutamate and substance P coexist in primary afferent terminals in the superficial laminae of spinal cord. *Proc Natl Acad Sci USA* **85**, 8720-8724. [Immunocytochemical assessment of the superficial dorsal horn demonstrated that substance P and glutamate were co-localized, indicating the possibility of co-release of these neuromediators from the same primary afferent terminal.]

DeHaven-Hudkins D.L., Dolle R.E. (2004) Peripherally restricted opioid agonists as novel analgesic agents. *Curr Pharm Des* **10**, 743-757. [Review of medicinal chemistry approaches that have been used to produce peripherally selective κ-opioid agonists.]

Devor M. (1999) Unexplain peculiarities of the dorsal root ganglion. *Pain* Suppl **6**, S27-S35. [Review of the role of the cell soma of primary afferent neurons in the dorsal root ganglion.]

Devor M. (2006) Sodium channels and mechanisms of neuropathic pain. *J Pain* **7** (Suppl 1), S3-S12. [Review on sodium channels and neuropathic pain within the context of the pain system.]

Devor M., Seltzer Z. (1999) Pathophysiology of damaged nerves in relation to chronic pain. in *Textbook of Pain* 4th ed. Wall P.D., Melzack R (eds) Churchill Livingstone, London, UK, pp. 129-164.

Dhami G.K., Ferguson S.S. (2006) Regulation of metabotropic glutamate receptor signaling, desensitization and endocytosis. *Pharmacol Ther* **111**, 260-271. [Review of the current understanding of the contribution of second messenger-dependent protein kinases, beta-arrestins and a novel Ral/phospholipase D2 (PLD2)-mediated endocytic pathway to the regulation of Group I mGluR endocytosis.]

Dib-Hajj S.D., Tyrrell L., Black J.A., Waxman S.G. (1998) NaN, a novel voltage-gated Na channel, is expressed preferentially in peripheral sensory neurons and down-regulated after axotomy *Proc Natl Acad Sci USA* **95**, 8963-8968. [Study demonstrating a preferential expression of NaN in DRG and trigeminal ganglia and the reduction of NaN mRNA levels in DRG after axonal injury, suggesting that NaN, together with SNS/PN3, may influence the generation of electrical activity in peripheral sensory neurons.]

Dickenson A.H. (1997) Plasticity: implications for opioid and other pharmacological interventions in specific pain states. *Behav Brain Sci* **20**, 392-403. [Review of the complex and contradictory findings on how the spinal effects of opioids can be altered in different pain states.]

Doubell T.P., Mannion R.H., Woolf C.J. (1999) The dorsal horn: state-dependent sensory processing, plasticity and the generation of pain. In *Textbook of Pain* 4th ed. Wall P.D. Melzack R. (eds) Churchill Livingstone, London, UK, pp. 165-181.

Dougherty P.M., Palecek J., Paleckova V., Sorkin L.S., Willis W.D. (1992) The role of NMDA and non-NMDA excitatory amino acid receptors in the excitation of primate spinothalamic tract neurons by mechanical, chemical, thermal, and electrical stimuli. *J Neurosci* **12**, 3025-3041. [Study showing a role for excitatory amino acids in the transmission of sensory information from primary afferent fibers to dorsal horn neurons and a role for NMDA receptors in the generation of hyperalgesia].

Dubner R. (2004) The neurobiology of persistent pain and its clinical implications. *Suppl Clin Neurophysiol* **57**, 3-7. [Review of neurobiology of persistent pain with a focus on the alteration of descending modulation of nociception following tissue injury.]

Duggan A.W., Riley R.C., Mark M.A., MacMillan S.J.A., Schaible H.G. (1995) Afferent volley patterns and the spinal release of immunoreactive substance P in the dorsal horn of the anaesthetized spinal cat. *Neurosci* **65**, 849-858. [Using microprobes bearing immobilized SP antibodies, paper shows maximal SP release from central terminals of primary afferent fibres occurs with relatively few impulses and at low frequencies in in a manner similar to that from peripheral terminals of these fibres.]

Dugowson C.E., Gnanashanmugam P. (2006) Nonsteroidal anti-inflammatory drugs. *Phys Med Rehabil Clin N Am* **17**, 347-354. [Review of nonsteroidal anti-inflammatory drugs, includes uses, side effects, toxicities and dosing and duration of therapy.]

Dunbar P.J., Chapman C.R., Buckley F.P., Gavrin J.R. (1996) Clinical analgesic equivalence for morphine and hydromorphone with prolonged PCA. *Pain* **68**, 265-270. [Clinical study showing that the analgesic equivalency ratio of hydromorphone to morphine is 3:1 for the treatment of oral mucositis in bone marrow transplant patients contrary to the widely accepted ratio of 7:1 determined from single dose studies.]

Dunlop J. (2006) Glutamate-based therapeutic approaches: targeting the glutamate transport system. *Curr Opin Pharmacol* **6**, 103-107. [Review of development of EAAT transporter inhibitors with improved subtype selectivity as tools for elucidating the contribution of each transporter subtype to the regulation of extracellular glutamate homeostasis and for the discovery of compounds capable of upregulating the activity of EAAT2.]

DuPen A., Shen D., Ersek M. (2007) Mechanisms of opioid-induced tolerance and hyperalgesia. *Pain Manag Nurs* **8**, 113-121. [Review of known and hypothesized pathological mechanisms surrounding the

phenomena of tolerance and hyperalgesia and their clinical implications.]

Ehret G.B., Desmeules J.A., Broers B. (2007) Methadone-associated long QT syndrome: improving pharmacotherapy for dependence on illegal opioids and lessons learned for pharmacology. *Expert Opin Drug Saf* **6**, 289-303. [Article summarizing factors influencing QT prolongation in patients taking methadone for treatment of opioid dependence.]

Evans H.C., Easthope S.E. (2003) Transdermal buprenorphine. *Drugs* **63**, 1999-2010. [Review of clinical pharmacology and analgesic effects of transdermal buprenorphine, including adverse effects.]

Fields H.L., Basbaum A.I., Heinricher M.M. (2006) Central nervous system mechanisms of pain modulation. In *Textbook of Pain* 5th ed. McMahon S.B., Koltzenberg M. (eds) Elsevier Churchill Livingstone, London, UK, pp. 125-142. [Overview of pain modulation focused primarily on the properties of a modulatory network with relays in the midbrain periaqueductal grey and rostral ventromedial medulla.

Finnerup N.B., Sindrup S.H., Jensen T.S. (2007) Chronic neuropathic pain: mechanisms, drug targets and measurement. Fundam *Clin Pharmacol* **21**, 129-136. [Review summarizes mechanisms of neuropathic pain, targets of currently used drugs, and measures used in neuropathic pain trials.]

Fishman S.M., Wilsey B., Mahajan G., Molina P. (2002) Methadone re-incarnated: novel clinical applications with related concerns. *Pain Med* **3**, 339-348. [Review of the clinical pharmacology and analgesic effects of methadone.]

Fitzgerald E.M., Okuse K., Wood J.N., Dolphin A.C., Moss S.J. (1999) cAMP-dependent phosphorylation of the tetrodotoxin-resistant voltage-dependent sodium channel SNS. *J Physiol* (London) **516**, 433-446. [Paper examining PKA phosphorylation of the cloned α-subunit of the rat sensory neurone-specific TTX-r channel SNS using site-directed mutagenesis, demonstrates that the removal of five PKA consensus sites strongly reduces the degree to which SNS is modulated by cAMP-dependent phosphorylation.]

Food and Drug Administration (1999) Over-the-counter drug products containing analgesic/ antipyretic active ingredients for internal use; required alcohol warning; final rule; compliance date. *Food and Drug Administration*, HHS, Fed Regist **64**, 13066-13067.

Fundytus M.E., Fisher K., Dray A., Henry J.L,. Coderre T.J. (1998) In vivo antinociceptive activity of anti-rat mGluR1 and mGluR5 antibodies in rats. *Neuroreport* **9**, 731-735. [Study involving intrathecal administration of antibodies raised against the C-terminals of mGluR1 and mGluR5 in various rat pain models, demonstrated that mGluRs are involved in nociceptive processing in persistent pain states but not acute pain signaling.]

Furuyama T., Kiyama H., Sato K., Park H.T., Maeno H., Takagi H., Tohyama M. (1993) Region-specific expression of subunits of ionotropic glutamate receptors (AMPA-type, KA-type and NMDA receptors) in the rat spinal cord with special reference to nociception. *Brain Res Mol Brain Res* **18**, 141-151. [Study in the rat showing that the subunit composition of AMPA-type receptors regulating motor neurons is different from that of AMPA-type receptors in the spinal sensory neurons, and that there are at least two types of glutamergic systems which regulate motor neurons: via AMPA-type receptors and via NMDA receptors.

Galer B.S., Harle J., Rowbotham M.C. (1996) Response to intravenous lidocaine infusion predicts subsequent response to oral mexiletine: a prospective study. *J Pain Symptom Manage* **12**, 161-167. [Clinical trial in patients with neuropathic pain showing that response to intravenous lignocaine infusions successfully predicts subsequent response to oral mexiletine.]

Gardner J.S., Blough D., Drinkard C.R., Shatin D., Anderson G., Graham D., Alderfer R. (2000) Tramadol and seizures: a surveillance study in a managed care population. Pharmacotherapy **20**, 1423-1431. [Study defined the risk of tramadol-associated seizures and factors that may increase the risk.]

Garry E.M., Fleetwood-Walker S.M. (2004) A new view on how AMPA receptors and their interacting proteins mediate neuropathic pain. *Pain* **109**, 210-213. [Review implicating intracellular docking proteins and AMPA receptors in chronic neuropathic pain.]

Gee N.S., Brown J.P., Dissanayake V.U., Offord J., Thurlow R., Woodruff G.N. (1996) The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. *J Biol*

Chem **271**, 5768-5776. [First study to provide evidence that the mechanism of action of gabapentin is via interaction with alpha2delta subunit of a calcium channel.]

George S.R., Fan T., Xie Z., Tse R., Tam V., Varghese G., O'Dowd B.F. (2000) Oligomerization of mu- and delta-opioid receptors. Generation of novel functional properties. *J Biol Chem* **275**, 26128-26135. [Study showing that the in vitro pharmacological properties of the mu-delta opioid receptor heterodimer are distinctly different from those of the individually expressed parent mu and delta opioid receptors.]

Gidal B., Billington R. (2006) New and emerging treatment options for neuropathic pain. *Am J Manag Care* **12**, S269-S278. [Review of treatments in development as well as existing agents for the symptomatic relief of neuropathic pain.]

Gillen C., Haurand M., Kobelt D.J., Wnendt S. (2000) Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor. *Nauyn Schmiedebergs Arch Pharmacol* **362**, 116-121. [First study to define the binding of tramadol hydrochloride [(1RS,2RS)-2-[(dimethyl-amino)-methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride] and its metabolites M1, M2, M3, M4 and M5 at the cloned human mu-opioid receptor and to show that the metabolite (+)-M1 is responsible for the mu-opioid-derived analgesic effect.]

Gogas K.R. (2006) Glutamate-based therapeutic approaches: NR2B receptor antagonists. *Curr Opin Pharmacol* **6**, 68-74. [Review of the data underpinning the development of NR2B subunit-containing NMDA receptors as potential novel therapeutics for treatment of neurodegenerative disorders.]

Gold M.S., Reichling D.B., Schuster M.J., Levine J.D. (1996) Hyperalgesic agents increase a tetrodotoxin-resistant Na+ current in nociceptors. *Proc Natl Acad Sci USA* **93**, 1108-1112. [Study showing that agents that produce hyperalgesia, i.e. prostaglandin E2, adenosine, and serotonin, can modulate tetrodotoxin (TTX)-resistant sodium current suggesting that modulation of TTX-resistant sodium current may be a mechanism for sensitization of nociceptors.]

Gold M.S., Levine J.D., Correa A.M. (1998) Modulation of TTX-R INa by PKC and PKA and their role in PGE2-induced sensitization of rat sensory neurons in vitro. *J Neurosci* **18**, 10345-10355. [Electrophysiological study in isolated sensory neurons showing that PKC activity is necessary to enable subsequent PKA-mediated modulation of tetrodotoxin (TTX)-resistant sodium current.]

Gold M.S. (1999) Tetrodotoxin -resistant Na+ currents and inflammatory hyperalgesia. *Proc Natl Acad Sci USA* **96**, 7645-7649. [Review of evidence supporting a role for tetrodotoxin (TTX)-resistant Na^+ currents in the sensitization of primary afferent neurons and inflammatory-induced hyperalgesia.]

Gold M.S., Weinreich D., Kim C.S., Wang R., Treanor J., Porreca F., Lai J. (2003) Redistribution of Na(V)1.8 in uninjured axons enables neuropathic pain. *J Neurosci* **23**, 158-166. [Study demonstrating that Na(V)1.8 expression increases in unmyelinated axons along the sciatic nerve and that attenuation of Na(V)1.8 expression prevented the redistribution of Na(V)1.8 in the sciatic nerve and reversed sciatic nerve ligation-induced neuropathic pain.]

Gomes I., Jordan B.A., Gupta A., Trapaidze N., Nagy V., Devi L.A. (2000) Heterodimerization of mu and delta opioid receptors: A role in opiate synergy. *J Neurosci* **20**, RC110. [*In vitro* study demonstrating that mu-delta opioid receptor heterodimers have distinctly different binding and functional characteristics relative to the parent mu and delta opioid receptors.]

Grond S., Sablotzki A. (2004) Clinical pharmacology of tramadol. *Clin Pharmacokinet* **43**, 879-923. [Review of the analgesic, pharmacokinetic and adverse effects of tramadol.]

Guo W., Zou S., Tal M., Ren K. (2002) Activation of spinal kainate receptors after inflammation: behavioral hyperalgesia and subunit gene expression. *Eur J Pharmacol* **452**, 309-318. [Study showing that the neural response to CFA-induced inflammation and hyperalgesia involves the activation of GluR5 and GluR6 subunits of kainate receptors.]

Guo W., Robbins M.T., Wei F., Zou S., Dubner R., Ren K. (2006) Supraspinal brain-derived neurotrophic factor signalling: A novel mechanism for descending pain facilitation. *J Neurosci* **26**, 126-137. [Paper demonstrating that BDNF-tyrosine kinase receptor B (TrkB) signaling in the descending pain pathway (PAG/RVM) contributes to pain facilitation in an NMDA-dependent manner.]

Hall E.J., Sykes N.P. (2004) Analgesia for patients with advanced disease: 1. *Postgrad Med J* **80**, 148-154. [This article discusses epidemiology, definitions, pathophysiology, assessment, non-pharmacological

approaches to pain management, the analgesic "ladder", and opioids.]

Hanani M. (2005) Satellite glial cells in sensory ganglia: from form to function. *Brain Res Brain Res Rev* **48**, 457-476. [Review of recent information on the physiology and pharmacology of satellite glial cells.]

Harris D.S., Mendelson J.E., Lin E.T., Upton R.A., Jones R.T. (2004) Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with naloxone: lack of dose proportionality. *Clin Pharmacokinet* **43**, 329-340. [In opioid-experienced volunteers, there were less than dose-proportional increases in plasma buprenorphine concentrations were proposed to contribute to the observed plateau for most pharmacodynamic effects as the dose is increased.]

Heiskanen T., Kalso E. (1997) Controlled-release oxycodone and morphine in cancer related pain. *Pain* **73**, 37-45. [In a randomized controlled study in patients with cancer pain, the total opioid consumption ratio of oxycodone to morphine was 2:3 when oxycodone was administered first, and 3:4 when oxycodone was administered after morphine. Significantly more vomiting occurred with morphine, whereas constipation was more common with oxycodone.]

Heiskanen T., Olkkola K.T., Kalso E. (1998) Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. *Clin Pharmacol Ther* **64**, 603-611. [A randomized double-blind crossover study in healthy human CYP2D6 extensive metabolizers pre-treated with quinidine on one occasion or placebo on another showed that a quinidine-induced significant reduction in plasma oxymorphone levels did not significantly alter the pharmacodynamic effects of oxycodone.]

Heppenstall P.A., Lewin G.R. (2001) BDNF but not NT-4 is required for normal flexion reflex plasticity and function. *Proc Natl Acad Sci USA* **98**, 8107-8112. [Study utilising a spinal cord preparation from BDNF and NT-4 knockout mice demonstrating a direct role for presynaptic BDNF release from sensory neurons in the modulation of pain-related neurotransmission.]

Hill D.R., Shaw T.M., Graham W., Woodruff G.N. (1990) Autoradiographical detection of cholecystokinin A receptors in primate brain using ^{125}I Bolton Hunter CCK 8 and ^{3}H MK329. *J Neurosci* **10**, 1070-1081. [Study using in vitro autoradiography to show that CCK-A receptors in primate brain may be involved in the processing of sensory information from the gut, the regulation of hormone secretion, and the activity of dopamine cell activity.]

Hogg R.C., Bertrand D. (2007) Partial agonists as therapeutic agents at neuronal nicotinic acetylcholine receptors. *Biochem Pharmacol* **73**, 459-468. [This review discusses the pharmacological properties of partial agonists and recent research developments in the field of partial agonists acting at nicotinic receptors.]

Hokfelt T. (1991) Neuropeptides in perspective – The last 10 years. *Neuron* **7**, 867-879. [Review of the scientific investigation of neuropeptides, including synthesis, localisation, role in neuronal plasticity and potential for development as therapeutic compounds.]

Hollmann M., Heinemann S. (1994) Cloned glutamate receptors. *Ann Rev Neurosci* **17**, 31-108. [Comprehensive review of the cloned glutamate receptors, including ligands, function and location.]

Hong S., Morrow T.J., Paulson P.E., Isom L.L., Wiley J.W. (2004) Early painful diabetic neuropathy is associated with differential changes in tetrodotoxin-sensitive and -resistant sodium channels in dorsal root ganglion neurons in the rat. *J Biol Chem* **279**, 29341-29350. [Study showing significant increases in the expression of Na(v)1.3 and Na(v) 1.7 and decreases in the expression of Na(v) 1.6 and Na(v)1.8 in DRG neurones from streptozotocin-induced diabetic rats and increased phosphorylation of Na(v)1.6 and Na(v)1.8. These results suggest that both TTX-S and TTX-R sodium channels play important roles and that differential phosphorylation of sodium channels contributes to painful diabetic neuropathy.]

Honig S., Murray K.A. (1984) An appraisal of codeine as an analgesic: single-dose analysis. *J Clin Pharmacol* **24**, 96-102. [Clinical study of single dose, codeine versus acetaminophen in the post-operative setting. This paper also provides a review the literature highlighting the difficulty in unequivocally establishing the value of codeine as an analgesic, in acceptable oral doses, in the single dose setting.]

Horn E., Nesbit S.A. (2004) Pharmacology and pharmacokinetics of sedatives and analgesics. *Gastrointest Endosc Clin N Am* **14**, 247-268. [Review of the pharmacology and pharmacokinetic properties of opioids with special emphasis on use in patients undergoing endoscopic procedures.]

Hoskin P.J., Hanks G.W., Aherne G.W., Chapman D., Littleton P., Filshie J. (1989) The bioavailability

and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *Br J Clin Pharmacol* **27**, 499-505. [Study undertaken in healthy volunteers of the oral and buccal bioavailability of morphine tablets showed route dependent differences in the morphine to morphine-6-glucuronide AUC ratios.]

Hur C., Chan A.T., Tramontano A.C., Gazelle G.S. (2006) Coxibs versus combination NSAID and PPI therapy for chronic pain: an exploration of the risks, benefits, and costs. *Ann Pharmacother* **40**, 1052-1063. [Systematic review comparing combination therapy with a nonselective NSAID and PPI relative to coxibs reported that both treatment paradigms provided equivalent pain control but coxibs have a lower GI tract complication profile but at an unknown increased risk of cardiovascular events and a greater financial cost.]

Ibrahim M.M., Rude M.L., Stagg N.J., Mata H.P., Lai J., Vanderah T.W., Porreca F., Buckley N.E., Makriyannis A., Malan T.P. Jr (2006) CB2 cannabinoid receptor mediation of antinociception. *Pain* **122**, 36-42. [Study using CB2 knockout mice to confirm the therapeutic potential of CB2 cannabinoid receptor agonists for the treatment of acute pain.]

Inturrisi C.E. (2002) Clinical pharmacology of opioids for pain. *Clin J Pain* **18** (Suppl), S3-13. [Comprehensive review of the clinical pharmacology of opioids for the management of pain; topics covered include opioid receptors, opioids (endogenous and exogenous), pharmacokinetics, issues related to opioid rotation, tolerance and dependence, as well as advantages and disadvantages of opioids for the management of pain.]

Isaac J.T., Mellor J., Hurtado D., Roche K.W. (2004) Kainate receptor trafficking: physiological roles and molecular mechanisms. *Pharmacol Ther* **104**, 163-172. [Review summarizes the current state of knowledge on the molecular mechanisms of kainate receptor trafficking and the potential for these mechanisms to regulate neuronal kainate receptor function.]

Jarvis B., Coukell A.J. (1998) Mexiletine. A review of its therapeutic use in painful diabetic neuropathy. *Drugs* **56**, 691-707. [Review of the clincal pharmacology and pharmacokinetics of mexiletine for symptomatic management of painful diabetic neuropathy in humans.]

Ji R.R., Woolf C.J. (2001) Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. *Neurobiol Dis* **8**, 1-10. [Review of central sensitization.]

Jiraki K. (1992) Lethal effects of normeperidine. *Am J Forensic Med Pathol* **13**, 42-43. [A single case study of the lethal effects of normeperidine in a patient with renal failure who had abused meperidine.]

Johnson R.E., Fudala P.J., Payne R. (2005) Buprenorphine: considerations for pain management. *J Pain Symptom Manage* **29**, 297-326. [Review summarizing the partial mu-agonist pharmacology of buprenorphine compared with full mu-opioid agonists.]

Jonker J.W., Wagenaar E., van Deemter L., Gottschlich R., Bender J.M., Dasenbrock J., Schinkel A.H. (1999) Role of blood-brain barrier P-glycoprotein in limiting brain accumulation and sedative side-effects of asimadoline, a peripherally acting analgesic drug. *Br J Pharmacol* **127**, 43-50. [Study in mdr1a/1b double knockout mice showing the absence of P-gp leads to a 9 fold increase in brain asimadoline accumulation without impairing the oral uptake of asimadoline.]

Jonsson K.O., Holt S., Fowler C.J. (2006) The endocannabinoid system: current pharmacological research and therapeutic possibilities. *Basic Clin Pharmacol Toxicol* **98**, 124-134. [Mini-review of the pharmacology of the endocannabinoid system including mechanism of action, identification of the endocannabinoid(s) involved in retrograde signalling, mechanism(s) of endocannabinoid uptake and biologically active metabolites of the endocannabinoids.]

Jordan B.A., Devi L.A. (1999) G-protein-coupled receptor heterodimerization modulates receptor function. *Nature* **399**, 697-700. [Seminal study describing biochemical and pharmacological evidence for the heterodimerization of two fully functional opioid receptors, kappa and delta resulting in a heterodimeric opioid receptor complex whose ligand binding and functional properties are distinctly different from those of either parent opioid receptor.]

Joshi S.K., Mikusa J.P., Hernandez G., Baker S., Shieh C.C., Neelands T., Zhang X.-F., Niforatos W., Kage K., Han P., Krafte D., Faltynek C., Sullivan J.P., Jarvis M.F., Honore P. (2006) Involvement of the TTX-resistant sodium channel Nav1.8 in inflammatory and neuropathic, but not post-operative, pain

states. *Pain* **123**, 75-82. [Study in rats showing antisense oligodeoxynucleotides targeting the Nav 1.8 sodium channel decreased mechanical allodynia following CFA-induced inflammation and chronic constriction injury of the sciatic nerve but did not alter mechanical allodynia in a vincristine chemotherapy-induced neuropathic pain model or a skin-incision model of post-operative pain.]

Kalso E., Poyhia R., Onnela P., Linko K., Tigerstedt I., Tammisto T. (1991) Intravenous morphine and oxycodone for pain after abdominal surgery. *Acta Anaesthesiol Scand* **35**, 642-646. [A clinical study showing that in post-surgical patients, intravenous oxycodone was more potent, had a faster onset and longer duration of analgesic action than intravenous morphine.]

Khaliq W., Alam S., Puri N. (2007) Topical lidocaine for the treatment of postherpetic neuralgia. *Cochrane Database Syst Rev* **Apr 18**(2):CD004846. [A meta-analysis of clinical trials to examine the efficacy and safety of topical lidocaine in the treatment of postherpetic neuralgia.]

King T., Ossipov M.H., Vanderah T.W., Porreca F., Lai J. (2005) Is paradoxical pain induced by sustained opioid exposure an underlying mechanism of opioid antinociceptive tolerance? *Neurosignals* **14**, 194-205. [Review of the evidence that prolonged opioid exposure enhances a descending pain facilitatory pathway from the RVM that is mediated at least in part by CCK activity and is essential for the maintenance of antinociceptive tolerance.]

Knotkova H., Pappagallo M. (2007) Adjuvant analgesics. *Med Clin N Am* **91**, 113-124. [Review of clinically available adjuvants for pain management].

Ko S., Zhao M.G., Toyoda H., Qiu C.S., Zhuo M. (2005) Altered behavioral responses to noxious stimuli and fear in glutamate receptor 5 (GluR5)- or GluR6-deficient mice. *J Neurosci* **25**, 977-984. [Study that used GluR5 and GluR6 subunit knockout mice to show that GluR5 is the kainate subunit involved in capsaicin-evoked or inflammatory pain but GluR6 is the kainate subunit involved in fear-memory and lateral amygdala synaptic potentiation.]

Koltzenburg M., Lundberg L.E.R., Torebjork H.E. (1992) Dynamic and static components of mechanical hyperalgesia in human hairy skin *Pain* **51**, 207-220. [Study showing two types of mechanical hyperalgesia develop in human hairy skin, viz a dynamic component (brush-evoked pain, allodynia) signalled by large myelinated afferents and a static component (hyperalgesia to pressure stimuli) signalled by unmyelinated afferents.]

Kontinen V.K., Meert T.F. (2003) Predictive validity of neuropathic pain models in pharmacological studies with a behavioural outcome in the rat: A systematic review. In: *Proceedings of the 10th World Congress on Pain, Progress in Pain Rsearch and Management*, Vol 24. Dostrovsky J.O., Carr D.B., Koltzenburg M. (eds) IASP Press, Seattle, pp. 489-498. [Review of the validity of various rodent models of neuropathic pain with respect to accurately predicting efficacy or lack therof of various treatments used to alleviate neuropathic pain in humans.]

Kovelowski C.J., Ossipov M.H., Sun H., Lai T.P., Malan T.P., Porreca F. (2000) Supraspinal cholecystokinin may drive tonic descending facilitation mechanisms to maintain neuropathic pain in the rat. *Pain* **87**, 265-273. [Study in rats implicating descending nociceptive facilitatory pathways in the maintenance of neuropathic pain that appears to be dependent on CCK release, and that may be driven by sustained afferent input from injured peripheral nerves to brainstem sites.]

Krause J.E., DiMaggio D.A., McCarson K.E. (1995) Alterations in neurokinin 1 receptor gene expression in models of pain and inflammation. *Can J Physiol Pharmacol* **73**, 854-859. [Review of substance P and the neurokinin 1 (NK1) receptor expression in arthritic disease, including the effect of morphine pretreatment on substance P and NK1 receptor levels, with reference to mechanisms that may regulate substance P turnover and NK1 receptor sensitivity in models of pain and inflammation.]

Krzanowska E.K., Rossi G.C., Pasternak G.W., Bodnar R.J. (1998) Potency ratios of morphine and morphine-6beta-glucuronide analgesia elicited from the periaqueductal gray, locus coeruleus or rostral ventromedial medulla of rats. *Brain Res* **799**, 329-333. [Review summarizing the antinociceptive potency of morphine compared with its metabolite morphine-6beta-glucuronide in supraspinal sites in the rat brain.]

Kronenberg R.H. (2002) Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother* **16**, 27-35. [Review comparing the clinical pharmacology of ketamine with respect to various routes of administration and with special reference to

possible psychological adverse effects.]

Kupers R., Kehlet H. (2006) Brain imaging of clinical pain states: a critical review and strategies for future studies. *Lancet Neurol* **5**, 1033-1044. [Critical review of the limitations of most published reports of brain imaging and chronic pain with suggested strategies for future studies]

Kurrikoff K., Koks S., Matsui T., Bourin M., Arend A., Aunapuu M., Vasar E. (2004) Deletion of the CCK2 receptor gene reduces mechanical sensitivity and abolishes the development of hyperalgesia in mononeuropathic mice. *Eur J Neurosci* **20**, 1577-1586. [Study showing that CCK2 knockout mice (i) have increased expression of CCK1, delta and kappa opioid receptor, (ii) are hyposensitive to mechanical stimulation and (ii) don't develop allodynia after peripheral nerve injury but have increased spinal POMC expression. Together these data suggest that mechanical sensitivity and development of neuropathic pain are regulated by antagonistic interactions between CCK and opioid systems.]

Lai J., Ossipov M.H., Vanderah T.W., Malan T.P. Jr, Porreca F. (2001) Neuropathic pain: the paradox of dynorphin. *Mol Interv* **1**, 160-167. [Review of the biological roles of spinal dynorphin in neurotransmission with a particular focus on the effective treatment of chronic pain syndromes and of the development of antinociceptive tolerance.]

Lai J., Gold M.S., Kim C.S., Bian D., Ossipov M.H., Hunter J.C., Porreca F. (2002) Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, NaV1.8. *Pain* **95**, 143-152. [Rat study showing administration of specific antisense oligodeoxynucleotide to Nav1.8 reversed spinal nerve injury-induced neuropathic pain suggesting that Nav1.8 may be a suitable target for novel anti-neuropathic drugs due to its restricted distribution to sensory nerves.]

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dynorphin. *J Pharmacol Exp Ther* **299**, 6-11. [Review of the potential mechanisms through which dynorphin contributes to spinally mediated antinociception, as well its interaction with multiple sites on the NMDA receptor complex to produce nociception and potential toxicity.]

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progressive tactile hypersensitivity. *Pain* **77**, 49-57. [Study showing intermittent tactile stimulation of the CFA-induced inflamed hindpaw to induce inflammatory progressive tactile hypersensitivity is sensitive to morphine, and to a lesser extent NMDA and NK1 receptor antagonists.]

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Markman J.D., Philip A. (2007) Interventional approaches to pain management. *Med Clin North Am* **91**, 271-286. [Review of the evidence for use of interventional techniques for chronic pain management including challenges and practical issues.]

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Mayer D.J., Mao J., Holt J., Price D.D. (1999) Cellular mechanisms of neuropathic pain, morphine tolerance and their interactions. *Proc Natl Acad Sci USA* **96**, 7731-7736. [Review describes evidence of common neural mechanisms underlying hyperalgesia and morphine tolerance providing a scientific basis for improved pain management with opioid analgesics.]

McCartney C.J., Sinha A., Katz J. (2004) A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. *Anesth Analg* **98**, 1385-1400. [Systematic review showing that dextromethorphan and ketamine have significant immediate and preventive analgesic benefit in 67% and 58% of studies, respectively.]

McCleane G. (2003) Pharmacological management of neuropathic pain. *CNS Drugs* **17**, 1031-1043. [Review of comparative evidence for and against the use of various drug treatments for the relief of neuropathic pain.]

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that the CCK 2 antagonist L-365,260 does not augment the analgesic effect of morphine in subjects with chronic neuropathic pain.]

McCleane G. (2004) Cholecystokinin antagonists: A new way to improve the analgesia from old analgesics? *Curr Pharm Des* **10**, 303-314. [Review examines the available evidence that suggests a role for CCK antagonists in human pain management.]

McCleane G. (2007) Topic analgesics. *Med Clin North Am* **91**, 125-139. [Review of agents that have been used topically for pain management.]

McLean M.J. (1994) Clinical pharmacokinetics of gabapentin. *Neurology* **44**(Suppl 5), S17-22. [Review of the unique clinical pharmacokinetic properties of gabapentin.]

McNicol E., Horowicz-Mehler N., Fisk R.A., Bennett K., Gialeli-Goudas M., Chew P.W., Lau J., Carr D.; Americal Pain Society (2003) Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain* **4**, 231-256. [Systematic review of clinical trials undertaken to assess the management of opioid side effects for the management of cancer pain or chronic noncancer pain.]

McQuay H.J., Tramer M., Nye B.A., Carroll D., Wiffen P.J., Moore R.A. (1996) A systematic review of antidepressants in neuropathic pain. *Pain* **68**, 217-227. [Systematic review of published clinical trials show that antidepressants are effective for the symptomatic relief of neuropathic pain.]

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Mellor J.R. (2006) Synaptic plasticity of kainate receptors. *Biochem Soc Trans* **34**, 949-951. [Review summarizing the evidence for the removal or insertion of functional kainate receptors in response to synaptic activity and the cellular mechanisms that underlie regulation of neuronal kainate receptor function.]

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Mico J.A., Ardid D., Berrocoso E., Eschalier A. (2006) Antidepressants and pain. *Trends Pharmacol Sci* **27**, 384-354. [Review of evidence supporting the hypothesis that pain and depression share common biochemical mechanisms and of the data supporting the notion that antidepressants have a genuine analgesic effect.]

Miguel R. (2000). Interventional treatment of cancer pain: the fourth step in the World Health Organization analgesic ladder? *Cancer Control* **7**,149-56.

Millan M.J. (1999) The induction of pain: an integrative review. *Prog Neurobiol* **57**, 1-164. [Review providing a global account of mechanisms involved in the induction of pain with particular attention focused on cellular aspects and on consequences of peripheral nerve injury.]

Milne R.W., Nation R.L., Somogyi A.A. (1996) The disposition of morphine and its 3- and 6-glucuronide metabolites in humans and animals, and the importance of the metabolites to the pharmacological effects of morphine. *Drug Metab Rev* **28**, 345-472. [Comprehensive review of the metabolism of morphine to active glucuronide metabolites and the contribution of these metabolites to the net pharmacology of systemically administered morphine.]

Moalem G., Tracey D.J. (2006) Immune and inflammatory mechanisms in neuropathic pain. *Brain Res Brain Res Rev* **51**, 240-264. [Brief review of studies implicating immune cells and inflammatory mediators in the development and maintenance of neuropathic pain.]

Munir M.A., Enany N., Zhang J.M. (2007) Nonopioid analgesics. *Med Clin North Am* **91**, 97-111. [Review of the use of paracetamol and NSAIDs as analgesics for the relief of various pain states.]

Murray A., Hagen N.A. (2005) Hydromorphone. *J Pain Symptom Manage* **29** (Suppl), S57-S66. [Review of the clinical use, pharmacokinetics and pharmacodynamics of hydromorphone with areas requiring further research attention to address remaining areas of uncertainty, highlighted.]

Moulin D.E., Palma D., Watling C., Schulz V. (2005) Methadone in the management of intractable neuropathic noncancer pain. *Can J Neurol Sci* **32**, 340-343. [Clinical case series of noncancer pain patients treated with oral methadone for a variety of intractable neuropathic pain states indicates that methodone may be especially useful in the management of intractable neuropathic pain.]

Nadal X., Banos J.E., Kieffer B.L., Maldonado R. (2006) Neuropathic pain is enhanced in delta-opioid receptor knockout mice. *Eur J Neurosci* **23**, 830-834. [DOR knockout mice with partial ligation of the sciatic nerve showed enhanced development of mechanical and thermal allodynia, and thermal hyperalgesia, suggesting a potential therapeutic use for DOR agonists for relief of neuropathic pain.]

Nassar M.A., Stirling L.C., Forlani G., Baker M.D., Matthew E.A., Dickenson A.H., Wood J.N. (2004) Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and nflammatory pain. *Proc Natl Acad Sci USA* **101**, 12706-12711. [Study used the Cre (Na(v)1.8) recombinase- loxP (Na(v)1.7) conditional knockout technique to produce nociceptor-specific Na(v)1.7 knockout mice that exhibited increased mechanical and thermal pain thresholds but with a decrease in all inflammatory pain responses evoked by a range of stimuli, such as formalin, carrageenan, complete Freund's adjuvant, or nerve growth factor.]

Nassar M.A., Levato A., Stirling L.C., Wood J.N. (2005) Neuropathic pain develops normally in mice lacking both Nav1.7 and Nav1.8. *Mol Pain* **1**, 24-32. [Study using sodium channel Na(v)1.7 knockout mice or Na(v)1.7 and Na1.8 double knockout mice to demonstrate that the development of neuropathic pain does not require the presence of either Nav1.7 or Nav1.8 alone or in combination whereas Nav1.7 is highly significant in determining inflammatory pain thresholds.]

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Novakovic S.D., Tzoumaka E., McGivern J.G., Haraguchi M., Sangameswaran L., Gogas K.R., Eglen R.M., Hunter J.C. (1998) Distribution of the tetrodotoxin-resistant sodium channel PN3 in rat sensory neurons in normal and neuropathic conditions. *J Neurosci* **18**, 2174-2187. [Study suggesting that specific subcellular redistribution of PN3 after peripheral nerve injury may be an important factor in establishing peripheral nerve hyperexcitability and resultant neuropathic pain.]

Obata K., Noguchi K. (2006) BDNF in sensory neurons and chronic pain. *Neurosci Res* **55**, 1-10. [Review of studies documenting contribution of the upregulation of brain-derived-neurotrophic-factor (BDNF) in dorsal root ganglia and spinal cord to development of hypersensitivity in chronic pain states thereby suggesting that blocking BDNF may be a fruitful strategy for the development of novel pain therapeutics.]

Okada Y., Tsuda Y., Bryant S.D., Lazarus L.H. (2002) Endomorphins and related opioid peptides. *Vitam Horm* **65**, 257-279. [Review of the endogenous opioid system focussing on the potential for development of unique opioid analgesics with minimal abuse potential and side-effects.]

Okuse K., Chaplan S.R., McMahon S.B., Luo Z.D., Calcutt N.A., Scott B.P., Akopian A.N., Wood J.N. (1997) Regulation of expression of the sensory neuron-specific sodium channel SNS in inflammatory and neuropathic pain. *Mol Cell Biol* **10**, 196-207. [Study in rat models of inflammatory and neuropathic pain indicating that the SNS (PN1) sodium channel is unlikely to underlie sensory neuron hyperexcitability associated with inflammation wheras reduced SNS (PN1) transcript levels were shown to be associated with peripheral nerve damage.]

Okuse K. (2007) Pain signalling pathways: From cytokines to ion channels. *Int J Biochem Cell Biol* **39**, 490-496. [Review of the currently available information on the molecular aspects of pain signalling pathways including novel and promising therapeutic targets for the treatment of pain in humans.]

Omana-Zapata I., Khabbaz M.A., Hunter J.C., Bley K.R. (1997) QX-314 inhibits ectopic nerve activity associated with neuropathic pain. *Brain Res* **771**, 228-237. [Study in rats implicating Na^+ channel accumulation in the generation of ectopic discharges in dorsal root ganglia and neuromas after sciatic nerve transection and showing that intravenous administration of the positively charged lidocaine derivative, QX-314, acutely blocks Na^+ channels at these sites.]

Ossipov M.H., Lai J., Vanderah T.W., Porreca F. (2003) Induction of pain facilitation by sustained opioid exposure: relationship to opioid antinociceptive tolerance. *Life Sci* **73**, 783-800. [Review describing systems-level adaptive changes induced by sustained opioid exposure resulting in pain due to descending facilitation, upregulation of spinal dynorphin and enhanced release of excitatory transmitters from primary afferents.]

Paar W.D., Frankus P., Dengler J.H. (1992) The metabolism of tramadol by human liver microsomes. *Clin Invest* **70**, 708-710. [Study of the in vitro metabolism of tramadol in human liver microsomes.]

Pace M.C., Mazzariello L., Passavanti M.B., Sansone P., Barbarisi M., Aurilio C. (2006) Neurobiology of pain. *J Cell Physiol* **209**, 8-12. [Review of the mechanisms implicated in the maintenance of pain and in inducing NMDA and AMPA receptor gene expression after prolonged inflammation.]

Pacher P., Batkai S., Kunos G. (2006) The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev* **58**, 389-462. [Comprehensive overview on the current state of knowledge of the endocannabinoid system as a target of pharmacotherapy.]

Pan Y.X., Xu J., Bolan E., Chang A., Mahurter L., Rossi G., Pasternak G.W. (2000) Isolation and expression of a novel alternatively spliced mu opioid receptor isoform, MOR-1F. *FEBS Lett* **466**, 337-340. [Study describing the isolation and characterisation a seventh MOR-1 gene splice variant, MOR-1F, which has selectivity for mu opioid ligands.]

Perea G., Araque A. (2005) Glial calcium signaling and neuron-glia communication. *Cell Calcium* **38**, 375-382.

Petrenko A.B., Yamakura T., Baba H., Shimoji K. (2003) The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg* **97**, 1108-1116. [Review of the role of NMDARs in pain in the context of subunit composition, particularly focusing on the importance of the NR2B subunit and its potential as a target for development of novel pain therapeutics.]

Pezet S., Cunningham J., Patel J., Grist J., Gavazzi I., Level I.J., Malcangio M. (2002a) BDNF modulates sensory neuron synaptic activity by a facilitation of GABA transmission in the dorsal horn. *Moll Cell Neurosci* **21**, 51-62. [Study using using in vitro and in vivo methods to show that exogenous BDNF can indirectly modulate primary sensory neuron synaptic efficacy via facilitation of the release of GABA from dorsal horn interneurons.]

Pezet S., Malcangio M., McMahon S.B. (2002c) BDNF: a neuromodulator in nociceptive pathways? *Brain Res Brain Res Rev* **40**, 240-249. [Review of the potential role of brain-derived neurotrophic factor as a neuromodulator in the spinal dorsal horn.]

Pezet S., McMahon S.B. (2006) Neurotrophins: mediators and modulators of pain. *Annu Rev Neurosci* **29**, 507-538. [Review of the evidence implicating NGF as a peripheral pain mediator and its regulation of BDNF from nociceptors and central terminals of peripheral nerves.]

Picard N., Cresteil T., Djebli N., Marquet P. (2005) In vitro metabolism study of buprenorphine: evidence for new metabolic pathways. *Drug Metab Dispos* **33**, 689-695. [Study using human liver microsomes and Ad293 P450-transfected cell lines as well as CYP3A4 and CYP2C8 recombinant isoforms to identify the human hepatic CYPs involved in the metabolism of buprenophine.]

Pick C.G., Peter Y., Schreiber S., Weizman R. (1997) Pharmacological characterization of buprenorphine, a mixed agonist-antagonist with kappa 3 analgesia. *Brain Res* **744**, 41-46. [Behavioural study in rats suggesting that buprenorphine produces antinociception as a partial mu receptor agonist as well as through an interaction with kappa-3 opioid receptors and to a lesser extent with kappa 1 opioid receptors.]

Plummer J.L., Gourlay G.K., Cmielewski P.L., Odontiadis J., Harvey I. (1995) Behavioural effects of norpethidine, a metabolite of pethidine, in rats. *Toxicology* **95**, 37-44. [Behavioural study in rats of the pethidine metabolite, norpethidine, indicates that its neurotoxic effects are unlikely to involve dopaminergic or cholinergic pathways.]

Porreca F., Lai J., Bian D., Wegert S., Ossipov M.H., Eglen R.M., Kassotakis L., Novakovic S., Robert D.K., Sangameswaran L., Hunter J.C. (1999) A comparison of the potential role of the tetrodotoxin-insensitive sodium channels, PN3/SNS and NaN/SNS2, in rat models of chronic pain. *Proc Natl Acad Sci USA* **96**, 7640-7644. [Study implicating Nav1.8 (PN3) sodium channels in chronic inflammatory or neuropathic pain suggesting that selective blockade of this target, in light of its restricted distribution to sensory neurons, might offer effective pain relief without a significant side-effect liability.]

Poyhia R., Olkkola K.T., Seppala T., Kalso E. (1991) The pharmacokinetics of oxycodone after intravenous injection in adults. *Br J Clin Pharmacol* **32**, 516-518. [Study describing the clinical pharmacokinetics of oxycodone after i.v. injection to healthy young adult surgical patients.]

Poyhia R., Seppala T., Olkkola K.T., Kalso E. (1992) The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. *Br J Clin Pharmacol* **33**, 617-621. [Crossover study undertaken in healthy volunteers to define the pharmacokinetics and metabolism of single oral and intramuscular bolus doses of oxycodone.]

Priest B.T., Murphy B.A., Lindia J.A., Diaz C., Abbadie C., Ritter A.M., Liberator P., Lyer L.M., Kash S.F., Kohler M.G., Kaczorowski G.J., MacIntyre D.E., Martin W.J. (2005) Contribution of the tetrodotoxin-resistant voltage-gated sodium channel $Na_v1.9$ to sensory transmission and nociceptive behaviour. *Proc Natl Acad Sci USA* **102**, 9382-9387. [Study using electrophysiological and behavioral methods in mice with a disruption of the SCN11A gene that encodes the NaV1.9 sodium channel, to suggest that inflammatory mediators modify the function of NaV1.9 to maintain inflammation-induced hyperalgesia.]

Raivich G. (2005) Like cops on the beat: the active role of resting microglia. *Trends Neurosci* **28**, 571-573. [Overview of the role of microglia in the normal and the injured brain.]

Rami H.K., Gunthorpe M.J. (2004) The therapeutic potential of TRPV1 (VR1) antagonists. *Drug Discov Today: Therapeutic Strategies* **1**, 97-104. [Review highlighting key evidence for targeting TRPV1 receptors for the treatment of persistent inflammatory and neuropathic pain as well as a range of other debilitating conditions.]

Rapp S.E., Egan K.J., Ross B.K., Wild L.M., Terman G.W., Ching J.M. (1996) A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* **82**, 1043-1048. [Parallel group clinical trial undertaken in post-operative patients that assessed levels of analgesia and adverse event profiles of morphine relative to hydromorphone administered via patient-controlled analgesia devices.]

Remy C., Marret E., Bonnet F. (2006) State of the art of paracetamol in acute pain therapy. *Curr Opin Anaesthesiol* **19**, 562-565. [Review highlighting new insights into the mechanism of action of paracetamol (acetaminophen) and its use in therapeutics.]

Robinson S.E. (2002) Buprenorphine: an analgesic with an expanding role in the treatment of opioid addiction. *CNS Drug Rev* **8**, 377-390. [Review of the clinical and molecular pharmacology of buprenorphine, with an emphasis on its use for the treatment of opioid addiction.]

Rogers M., Tang L., Madge D.J., Stevens E.B. (2006) The role of sodium channels in neuropathic pain. *Semin Cell Dev Biol* **17**, 571-581. [Review of current understanding of the roles of sodium channels in pain and nociceptive information processing, with a particular emphasis on neuropathic pain and drugs useful for the treatment of neuropathic pain that act through mechanisms involving block of sodium channels.]

Ross F.B., Wallis S.C., Smith M.T. (2000) Co-administration of sub-antinociceptive doses of oxycodone and morphine produces marked antinociceptive synergy with reduced CNS side-effects in rats *Pain* **84**, 421-428. [First study in rats to show that co-administration of sub-antinociceptive doses of oxycodone with morphine by intracerebroventricular or systemic routes, results in markedly increased (synergistic) levels of antinociception.]

Ruscheweyh R., Sandkühler J. (2002) Role of kainate receptors in nociception. *Brain Res Brain Res Rev*

40, 215-222. [Review of studies on the localization of kainate receptors in dorsal root ganglia and spinal dorsal horn and their physiological and pathophysiological importance particularly with regard to nociceptive pathways including a brief overview of the agonist and antagonist pharmacology].

Salerno L., Sorrenti V., Di Giacomo C., Romeo G,. Siracusa M.A. (2002) Progress in the development of selective nitric oxide synthase (NOS) inhibitors. *Curr Pharm Des* **8**, 177-200. [Review of recent developments of new molecules endowed with inhibitory properties against the various isoforms of NOS with a major focus on structure-activity-selectivity relationships especially concerning compounds belonging to the non-amino acid-based inhibitors.]

Sangameswaran L., Delgado S.G., Fish L.M., Koch B.D., Jakeman L.B., Steward G.R., Sze P., Hunter J.C., Eglen R.M., Herman R.C. (1996) Additions and Corrections to Structure and function of a novel voltage-gated, tetrodotoxin-resistant sodium channel specific to sensory neurons. *J Biol Chem* **271**, 5953-5956. [First study to clone and assess functional expression of the α- subunit of a novel, voltage-gated, TTX-resistant sodium channel, PN3, which is expressed predominantly by small sensory neurons within the peripheral nervous system.]

Satkunanathan N., Livett B., Gayler K., Sandall D., Down J., Khalil Z. (2005) Alpha-conotoxin Vc1.1 alleviates neuropathic pain and accelerates functional recovery of injured neurones. *Brain Res* **1059**, 149-158. [Study showing that alpha-conotoxin Vc1.1, a neuronal nAChR antagonist, suppressed mechanical pain responses associated with peripheral neuropathy in rats and accelerated functional recovery of the injured neurones.]

Sawynok J. (2005) Topical analgesics in neuropathic pain. *Curr Pharm Des* **11**, 2995-3004. [Review of pathophysiology of neuropathic pain and agents with evidence of topical use for the management of neuropathic pain].

Schafer M., Zhou L., Stein C. (1998) Cholecystokinin inhibits peripheral opioid analgesia in inflamed tissue. *Neuroscience* **82**, 603-611. [Study in rats showing that activation of peripheral cholecystokinin B (CCK B) but not CCK A receptors attenuates the peripheral antinociceptive effects of μ-opioid agonists in inflamed tissue, possibly via a protein kinase C-dependent mechanism in sensory nerve terminals.]

Schaible H.-G., Grubb B.D. (1993) Afferent and spinal mechanisms of joint pain. *Pain* **55**, 5-54. [Extensive review of the mechanisms involved in the sensitization of joint afferents, in neural processing in the CNS and in neuroplasticity with respect to joint pain.]

Schaible H.G. (2007) Peripheral and central mechanisms of pain generation. *Handb Exp Pharmacol* **177**, 3-28. [Review of the neuronal mechanisms that underlie clinically relevant pain states such as inflammatory and neuropathic pain.]

Schoepp D.D., Jane D.E., Monn J.A. (1999) Pharmacological agents acting at subtypes of metabotropic glutamate receptors. *Neuropharmacology* **38**, 1431-1476. [Review of evolution of pharmacological agents targeting mGlu receptors, with a focus on known receptor subtype selectivities of current agents.]

Schulte G., Robertson B., Fredholm B.B., DeLander G.E., Shortland P., Molander C. (2003) Distribution of antinociceptive adenosine A1 receptors in the spinal cord dorsal horn, and relationship to primary afferents and neuronal subpopulations. *Neuroscience* **121**, 907-916. [Study using immunohistochemistry, in situ hybridization, radioligand binding and confocal microscopy to show that adenosine A1 receptors are localised in the postsynaptic neuronal cell bodies and processes of inner lamina II of the dorsal horn of the spinal cord, in close contact with structures important for modulation of nociceptive information.]

Scott D.A., Wright C.E., Angus J.A. (2002) Actions of intrathecal omega-conotoxins CVID, GVIA, MVIIA, and morphine in acute and neuropathic pain in the rat. *Eur J Pharmacol* **451**, 279-286. [Study undertaken a spinal nerve ligation model of neuropathic pain in the rat showing that the therapeutic window of spinally administered CVID, was superior to that of either MVIIA or GVIA.]

Sherrington C.S. (1906) The integrative action of the nervous system. Scribner, New York. [Seminal text written as a series of 10 lectures that changed the subsequent course of neurophysiology; re-published 3 times in 1920, 1947 & 1961.]

Sills G.J. (2006) The mechanisms of action of gabapentin and pregabalin. *Curr Opin Pharmacol* **6**, 108-113. [Review of the evidence in support of the notion that gabapentin and pregabalin produce their anti-neuropathic effects through selective inhibition of voltage-gated calcium channels containing the alpha2delta-1 subunit.]

Silverman J.D., Kruger L. (1988) Acid phosphatase as a selective marker for a class of small sensory ganglion cells in several mammals: spinal cord distribution, histochemical properties, and relation to fluoride-resistant acid phosphatase (FRAP) of rodents. *Somatonsens Res* **5**, 219-246. [Review of the visualization of FRAP-like activity in several nonrodent species, with reference to previous work indicating its presence only in mouse and rat, with the inclusion of technical factors, limitations and alternative interpretations.]

Simmons R.M., Li D..L, Hoo K.H., Deverill M., Ornstein P.L., Iyengar S. (1998) Kainate GluR5 receptor subtype mediates the nociceptive response to formalin in the rat. *Neuropharmacol* **37**, 25-36. [Study using compounds with varying activities at the AMPA and kainate receptor subtypes suggest an involvement of the GluR5 subunit in the processing of nociceptive information.]

Sindrup S.H., Graf A., Sfikas N. (2006) The NK1-receptor antagonist TKA731 in painful diabetic neuropathy: a randomised, controlled trial. *Eur J Pain* **10**, 567-571. [Multicenter, randomised, double-blind, placebo-controlled and parallel-group clinical trial showing that the non-peptide NK(1)-receptor antagonist TKA731, at 150 mg daily for 2 weeks did not produce significant pain relief above placebo in patients with painful diabetic polyneuropathy.]

Sindrup S.H., Jensen T.S. (1999) Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* **83**, 389-400. [Systematic review of currently available agents used to treat neuropathic pain including numbers needed to treat for particular agents in specific neuropathic pain sub-types].

Slack S.E., Pezet S., McMahon S.B., Thompson S.W., Malcangio M. (2004) Brain-derived neurotrophic factor induces NMDA receptor subunit one phosphorylation via ERK and PKC in the rat spinal cord. *Eur J Neurosci* **20**, 1769-1778. [Paper provides evidence to suggest that BDNF modulates the activity of the NMDA receptor by phosphorylation via the kinases ERK and PKC.]

Smith H., Elliott J. (2001) Alpha2 receptors and agonists in pain management. *Curr Opin Anaesthesiol* **14**, 513-518. [Review of the clinical utility of alpha2 receptor agonists in pain management.]

Smith H.S. (2006) Arachidonic acid pathways in nociception; *J Support Oncol* **4**, 277-287. [Review of the mechanisms contributing to various pain and inflammatory states, the metabolic fates of arachidonic acid, the functions of its many metabolites, and the interrelatedness of the various metabolic pathways involved in nociception with a view to optimising future pain treatments.]

Smith M.T., Cabot P.J., Ross F.B., Robertson A.D., Lewis R.J. (2002) The novel N-type calcium channel blocker, AM336, produces potent dose-dependent antinociception after intrathecal dosing in rats and inhibits substance P release in rat spinal cord slices. *Pain* **96**, 119-127. [First study documenting the antinociceptive effects of the N-type calcium channel blocker, AM336 (otherwise known as CVID) in a rat model of persistent pain and that AM336 likely produces its antinociceptive effects by inhibiting release of the pro-nociceptive neurotransmitter,substance P, in the spinal cord.]

Snyder S.H., Pasternak G.W. (2003) Historical review: Opioid receptors. *Trends Pharmacol Sci* **24**, 198-205. [Historical overview of investigations undertaken to characterize opioid receptor binding, localization and function.]

Somogyi A.A., Barratt D.T., Coller J.K. (2007) Pharmacogenetics of opioids. *Clin Pharmacol Ther* **81**, 429-444. [Review of genetic factors potentially modulating the pharmacokinetics (metabolizing enzymes, transporters) and pharmacodynamics (receptors and signal transduction elements) that contribute to interpatient variability in the response to opioids.]

Souslova V., Cesare P., Ding Y., Akopian A.N., Stanfa L., Suzuki R., Carpenter K., Dickenson A., Boyce S., Hill R., Nebenuis-Oosthuizen D., Smith A.J., Kidd E.J., Wood J.N. (2000) Warm-coding deficits and aberrant inflammatory pain in mice lacking P2X3 receptors. *Nature* **407**(6807): 1015-1017. [Paper showing that ablation of the P2X3 gene in mice results in the loss of rapidly desensitizing ATP-gated cation currents in dorsal root ganglion neurons and altered responses of nodose ganglion neurons to ATP as well as enhanced thermal hyperalgesia in these mice under conditions of chronic inflammation.]

South S.M., Smith M.T. (2001) Analgesic tolerance to opioids. *Pain – Clinical Updates* **9**, 1-4. [Brief review highlighting the common signalling pathways between analgesic tolerance to morphine and persistent pain.]

Srinivasan V., Wielbo D., Simpkins J., Karlix J., Sloan K., Tebbett I. (1996) Analgesic and

immunomodulatory effects of codeine and codeine 6-glucuronide. *Pharm Res* **13**, 296-300. [Study showing intracerebroventricular codeine-6-glucuronide, the major metabolite of systemically administered codeine, is a potent antinociceptive agent, suggesting that codeine-6-glucuronide may contribute to the analgesic effects of codeine.]

Standifer K.M., Pasternak G.W. (1997) G proteins and opioid receptor-mediated signalling. *Cell Signal* **9**, 237–248. [Review of in vivo and in vitro studies that have examined G-protein interactions with each of the opioid receptor subtypes.]

Stanley T.H. (2005) Fentanyl. *J Pain Symptom Manage* **29** (Suppl), S67-S71. [Review of the development and clinical use of fentanyl.]

Stubhaug A., Breivik J., Eide P.K., Kreunen M., Foss A. (1997) Mapping of punctate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand* **41**, 1124-1132. [Clinical study in patients showing that NMDA receptor blockade prevents central sensitization induced by nociceptive input during and after surgery.]

Subrahmanyam V., Renwick A.B., Walters D.G., Price R.J., Tonelli A.P., Lake B.G. (2001) Identification of cytochrome P-450 isoforms responsible for cis-tramadol metabolism in human liver microsomes. *Drug Metab Dispos* **29**, 1146-1155. [Study used human liver microsomes to show that cis-tramadol is metabolized to the tramadol metabolites, M1, M2, M3, and M5 via multiple CYP isoforms with hepatic CYP2D6 being primarily responsible for metabolism to M1 whereas M2 formation is catalyzed by both CYP2B6 and CYP3A4.]

Szekely J.I., Torok K., Mate G. (2002) The role of ionotropic glutamate receptors in nociception with special regard to the AMPA binding sites. *Curr Pharm Des* **8**, 887-912. [Review of the antinociceptive effects of ionotropic glutamate receptor antagonists, with emphasis on clinical potential.]

Taiwo Y.O., Goetzl E.J., Levine J.D. (1987) Hyperalgesia onset latency suggests a hierarchy of action. *Brain Res* **423**, 333-337. [Study assessing the temporal onset of hyperalgesia following intradermal administration of various inflammatory mediators in rats, showed that inflammatory mediators known to produce hyperalgesia via indirect mechanisms resulted in a significant delay in onset of hyperalgesia after intradermal administration.]

Tao R., Auerbach S.B. (1995) Involvement of the dorsal raphe but not median raphe nucleus in morphine-induced increases in serotonin release in the rat forebrain. *Neuroscience* **68**, 553-561. [In vivo microdialysis study showing that systemic morphine acting in the dorsal raphe nucleus, but not the median raphe nucleus, enhances serotonin release in specific forebrain sites, and that increases in serotonin release in dorsal raphe nucleus projection sites do not occur secondary to changes in behavioral state or body temperature.]

Tao F., Liaw W.J., Zhang B., Yaster M., Rothstein J.D., Johns R.A., Tao Y.X. (2004) Evidence of neuronal excitatory amino acid carrier 1 expression in rat dorsal root ganglion neurons and their central terminals. *Neuroscience* **123**, 1045-1051. [Immunohistochemical study indicating the presence of EAAC1 in dorsal root ganglion neurons and their central terminals, thereby suggesting that EAAC1 might play an important role in nociceptive neurotransmission via the regulation of pre-synaptically released glutamate.]

Tassone D.M., Boyce E., Guyer J., Nuzum D. (2007) Pregabalin: A novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther* **29**, 26-48. [Review summarizing the pharmacology, pharmacokinetics, efficacy, and tolerability of pregabalin, its approved use in the management of neuropathic pain and refractory partial-onset seizures; and the notion that it may be usefel as an adjunctive treatment for patients with generalized anxiety disorder or social anxiety disorder.]

Tate S., Benn S., Hick C., Trezise D., John V., Mannion RJ., Costigan M., Plumpton C., Grose D., Gladwell Z., Kendall G., Dale K., Bountra C., Woolf C.J. (1998) Two sodium channels contribute to the TTX-R sodium current in primary sensory neurons. *Nat Neurosci* **1**, 653-655. [First study to show that two distinct sodium channels, SNS2 and SNS/PN3, contribute to the TTX-R sodium current in small-diameter DRG neurons.]

Taylor C.P., Angelotti T., Fauman E. (2007) Pharmacology and mechanism of action of pregabalin: The

calcium channel alpha(2)-delta subunit as a target for antiepileptic drug discovery. *Epilepsy Res* **73**, 137-150. [Review summarizing the preclinical pharmacology of pregabalin, the biology of the high affinity binding site on the alpha(2)-delta subunit of calcium channels and pregabalin's presumed mechanism of action.]

Thompson S.W., Bennett D.L., Kerr B.J., Bradbury E.J., McMahon S.B. (1999) Brain-derived neurotrophic factor is an endogenous modulator of nociceptive responses in the spinal cord. *Proc Natl Acad Sci USA* **96**, 7714-7718. [Review summarizing how BDNF satisfies many of the criteria necessary to be regarded as a neurotransmitter/neuromodulator in small-diameter nociceptive neurons and implicating BDNF in sensory abnormalities associated with persistent inflammation.]

Todd A.J., Sullivan A.C. (1990) A light microscope study of the coexistence of GAA-like and glycine-like immunoreactivities in the spinal cord of the rat. *J Comp Neurol* **296**, 496-505. [Immunohistochemical study suggesting that the inhibitory neurotransmitters GABA and glycine coexist within cell bodies and axons in the rat spinal cord.]

Todd A.J., Spike R.C. (1993) The localization of classical transmitters and neuropeptides within neurons in laminae I-III of the mammalian spinal dorsal horn. *Prog Neurobiol* **41**, 609-646. [Review summarising the available information concerning transmitter and peptide content of neurons in lamina I-III of the dorsal horn of the mammalian spinal cord.

Todd A.J., Hughes D.I., Polgár E., Nagy G.G., Mackie M., Ottersen O.P., Maxwell D.J. (2003) The expression of vesicular glutamate transporters VGLUT1 and VGLUT2 in neurochemically defined axonal populations in the rat spinal cord with emphasis on the dorsal horn. *Eur J Neurosci* **17**, 13-27. [Immunohistochemical study in rats showing differential expression of vesicular glutamate transporters, VGLUT1 and VGLUT2, on various neurochemically-defined neuronal populations in the dorsal horn of the spinal cord.]

Todd A.J., Koerber J.R. (2006) Neuroanatomical substrates of spinal nociception. In: *Textbook of Pain* Eds McMahon SB and Koltzenburg M, 5th ed. pp. 73-90. [Overview of the neuroanatomical organization of nociceptive neurotransmission at the level of the spinal cord.]

Tölle T.R., Berthele A., Zieglgänsberger W., Seeburg P.H., Wisden W. (1993) The differential expression of 16 NMDA and non-NMDA receptor subunits in the rat spinal cord and in periaqueductal gray. *J Neurosci* **13**, 5009-5028. [Study that used *in situ* hybridization in rat lumbar spinal cord and the periaqueductal gray to assess the differential expression of 16 genes, encoding all known subunits for the NMDA receptor, AMPA/low-affinity kainate, high-affinity kainate ionotropic receptors and two orphan receptor subunits.]

Tominaga M., Caterina M.J., Malmberg A.B., Rosen T.A., Gilbert H., Skinner K,. Raumann B.E., Basbaum A.I., Julius D. (1998) The cloned capsaicin receptor integrates multiple pain-producing stimuli. *Neuron* **21**, 531-543. [Electrophysiological study in excised membrane patches showing that noxious heat gates VR1 (TRPV1) receptors and implicating VR1 receptors in injury-induced hypersensitivity at the level of the sensory neuron.]

Urban L., Thompson S.W.N., Dray A. (1994) Modulation of spinal excitability: co-operation between neurokinin and excitatory amino acid neurotransmitters. *Trends Neurosci* **17**, 432-438. [Overview of some of the mechanisms underpinning central hyperexcitability in hyperalgesia and allodynia based on evidence from both in vivo and in vitro experiments using neurokinin and N-methyl-D-aspartate receptor antagonists.]

Urban M.O., Zahn P.K., Gebhart G.F. (1999) Descending facilitatory influences from the rostral medial medulla mediate secondary, but not primary hyperalgesia in the rat. *Neuroscience* **90**, 349-352. [Study undertaken in rat models of primary and secondary hyperalgesia showing that descending nociceptive facilitatory influences from the rostral medial medulla significantly contribute to the development of secondary, but not primary, hyperalgesia.]

Vadalouca A., Siafaka I., Argyra E., Vrachnou E., Moka E. (2006) Therapeutic management of chronic neuropathic pain: an examination of pharmacologic treatment. *Ann N Y Acad Sci* **1088**, 164-186. [Review of recent advances in the therapeutic management of chronic neuropathic pain.]

Vane J.R. (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* **231**, 232-235. [Seminal paper defining the mechanism of action of NSAIDs.]

Vanegas H., Schaible H.G. (2004) Descending control of persistent pain: inhibitory or facilitatory? *Brain Res Brain Res Rev* **46**, 295-309. [Review of the evidence supporting the notion that persistent inflammatory and neuropathic pain simultaneously triggers descending facilitation and inhibition.]

Vincler M., Wittenauer S., Parker R., Ellison M., Olivera B.M., McIntosh J.M. (2006) Molecular mechanism for analgesia involving specific antagonism of alpha9alpha10 nicotinic acetylcholine receptors. *Proc Natl Acad Sci USA* **103**, 17880-17884. [Paper demonstrates the involvement of alpha9alpha10 nAChRs in the pathophysiology of peripheral nerve injury and the data implicate this receptor as a target for the treatment of neuropathic pain.]

Vree T.B., van Dongen R.T., Koopman-Kimenai P.M. (2000) Codeine analgesia is due to codeine-6-glucuronide, not morphine. *Int J Clin Pract* **54**, 395-398. [Study implicating codeine-6-glucuronide rather than morphine, as the analgesic metabolite of codeine.]

Vulchanova L., Riedl M.S., Shuster S.J., Buell G., Surprenant A., North R.A. Elde R. (1997) Immunohistochemical study of the P2X2 and P2X3 receptor subunits in rat and monkey sensory neurons and their central terminals. *Neuropharmacology* **36**, 1229-1242. [Study showing species differences in P2X2 and P2X3 localisation between rats and monkey and that these receptors are expressed differentially on sensory neurons in the dorsal root and nodose ganglia as well as the dorsal horn of the spinal cord.]

Walsh D. (2005) Advances in opioid therapy and formulations. *Support Care Cancer* **13**, 138-144. [Review of newer dosage forms and formulations for delivery of opioid treatment in humans.]

Watkins L.R., Hutchinson M.R., Ledeboer A., Wieseler-Frank J., Milligan E.D., Maier S.F. (2007) Norman Cousins Lecture. Glia as the "bad guys": implications for improving clinical pain control and the clinical utility of opioids. *Brain Behav Immun* **21**, 131-146. [Review of the role of glia in the development and maintenance of persistent pain states as well as the development of tolerance to the pain-relieving effects of opioid analgesics such as morphine and the possibility of developing new treatments targeted to activated glia as a means of improving pain management.]

Watson N., Linder M.E., Druey K.M., Kehrl J.H., Blumer K.J. (1996) RGS family members: GTPase-activating proteins for heterotrimeric G-protein α-subunits. *Nature* **383**, 172–175. [Study showing the mechanisms that govern the duration and specificity of physiological responses elicited by G-protein-mediated signalling pathways and that RGS proteins are likely to regulate a subset of the G-protein signalling pathways in mammalian cells.]

Whitcomb D., Block G. (1994) Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA* **272**, 1845-1850. [Retrospective case series studied to determine that acetaminophen hepatotoxicity after an overdose appears to be enhanced by fasting in addition to alcohol ingestion.]

Wiesenfeld-Hallin Z., Xu X.J., Hokfelt T. (2002) The role of spinal cholecystokinin in chronic pain states. *Pharmacol Toxicol* **91**, 398-403. [Review of the experimental evidence implicating cholecystokinin in persistent pain and hence its potential as a target for the development of novel pain therapeutics.]

Wiffen P.J., McQuay H.J., Moore R.A. (2005) Carbamazepine for acute and chronic pain. *Cochrane Database Syst Rev* **Jul 20**(3), CD005451. [Meta-analysis of clinical trials indicating that there is evidence to show that carbamazepine is effective even though the clinical trials are small.]

Willis W.D., Coggeshall R.E. (2004) Sensory mechanisms of the spinal cord. 3rd ed. Kluwer Academic/Plenum Publishers, New York. [Comprehensive book covering many topics relevant to pain.]

Wood J.N., Boorman J.P., Okuse K., Baker M.D. (2004) Voltage-gated sodium channels and pain pathways. *J Neurobiol* **61**, 55-71. [Review of the experimental data supporting the development of isotype-specific sodium channel blockers for the treatment of persistent pain.]

Woolf C.J., Costigan M. (1999) Transcriptional and posttranslational plasticity and the generation of inflammatory pain. *Proc Natl Acad Sci USA* **96**, 7723-7730. [Review of peripheral and central neuroplasticity secondary to induction of inflammation in peripheral tissues.]

Woolf C.J., King A.E. (1987) Physiology and morphology of multireceptive neurons with C-afferent fiber inputs in the deep dorsal horn of the rat lumbar spinal cord. *J Neurophysiol* **58**, 460-479. [Electrophysiological study defining the physiological properties and morphology of neurons that respond

to low- and to high-intensity mechanical stimulation of the skin of the rat hindpaw.]

Woolf C.J., Safieh-Garabedian B., Ma Q.-P., Crilly P., Winter J. (1994) Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity. *Neuroscience* **62**, 327-331. [Study showing that elevation in levels of the neurotrophin, NGF, in the periphery is a major contributor to CFA-induced inflammatory pain.]

Woolf C.J., Salter M.W. (2006) Plasticity and pain: role of the dorsal horn. In: *Textbook of Pain* Eds McMahon SB and Koltzenburg M, 5th ed. pp. 91-105. [Review of progress in elucidating the molecular and cellular mechanisms responsible for synaptic plasticity in the spinal cord.]

World Health Organisation (1986) Cancer Pain Relief. Geneva: WHO. [Booklet summarizing the guidelines developed by the World Health Organisation in collaboration with the International Association for the Study of Pain for the management of chronic cancer pain and encapsulated by the WHO Analgesic Ladder.]

Wotherspoon G., Fox A., McIntyre P., Colley S., Bevan S., Winter J. (2005) Peripheral nerve injury induces cannabinoid receptor 2 protein expression in rat sensory neurons. *Neuroscience* **135**, 235-245. [Study showing marked upregulation of cannabinoid CB2 receptor immunoreactivity in dorsal root ganglia and in laminae 1/2 of the dorsal horn of the spinal cord in mouse models of neuropathic pain, suggesting that the CB2 receptor may be a useful target for the development of novel anti-neuropathic pain medications].

Wright A.W., Mather L.E., Smith M.T. (2001) Hydromorphone-3-glucuronide: a more potent neuro-excitant than its structural analogue, morphine-3-glucuronide. *Life Sci* **69**, 409-420. [Comparative study of the neuro-excitatory pharmacology of hydromorphone-3-glucuronide (H3G) relative to morphine-3-glucuronide (M3G) in rats showing that following intracerebrventricular administration, H3G is approximately 2.5-fold more potent than M3G.]

Wu L.J., Ko S.W., Zhuo M. (2007) Kainate receptors and pain: from dorsal root ganglion to the anterior cingulated cortex. *Curr Pharm Des* **13**, 1597-1605. [Review of studies showing kainate receptors regulate nociceptive responses and highlighting them as a potential target for the development of novel treatments for management of chronic pain.]

Xu X.-J., Alster P., Wu W.-P., Hao J.-X., Wiesenfeld-Hallin Z. (2001) Increased level of cholecystokinin in cerebrospinal fluid is associated with chronic pain-like behaviour in spinally injured rats. *Peptides* **22**, 1305-1308. [Study showed that spinally injured rats which exhibit pain-like behaviours have elevated CSF levels of the anti-opioid peptide, cholecystokinin, relative to non-injured rats and spinally injured rats that don't exhibit pain-like behaviours.]

Xu H., Wu L.J., Zhao M.G., Toyoda H., Vadakkan K.I., Jia Y., Pinaud R., Zhuo M. (2006) Presynaptic regulation of the inhibitory transmission by GluR5-containing kainate receptors in spinal substantia gelatinosa. *Mol Pain* **2**, 29. [Study using pharmacological, electrophysiological and genetic methods in spinal cord slices to show that presynaptic GluR5 KARs are involved in the modulation of inhibitory transmission in the spinal substantia gelatinosa.]

Yajima Y., Narita M., Narita M., Matsumoto N., Suzuki T. (2002) Involvement of a spinal brain-derived neurotrophic factor/full-length TrkB pathway in the development of nerve injury-induced thermal hyperalgesia in mice. *Brain Res* **958**, 338-346. [Study in mice implicating BDNF but not neurotrophin-4 in the development of thermal hyperalgesia secondary to partial sciatic nerve ligation.]

Yaksh T.L. (2006) Central pharmacology of nociceptive transmission. In: *Textbook of Pain* Eds McMahon SB and Koltzenburg M, 5th ed. pp. 371-414. [Overview of the pharmacology associated with nociceptive neurotransmission at spinal and supraspinal sites.]

Yeung J.C., Rudy T.A. (1980) Multiplicative interaction between narcotic agonisms expressed at spinal and supraspinal sites of antinociceptive action as revealed by concurrent intrathecal and intracerebroventricular injections of morphine. *J Pharmacol Exp Ther* **215**, 633-642. [Study showing that the analgetic potency of intrathecal morphine is potentiated by concurrent administration of intracerebroventricular morphine and vice versa.]

Yu X.-M., Salter M.W. (1999) Src, a molecular switch governing gain control of synaptic transmission mediated by N-methyl-D-aspartate receptors. *Proc Natl Acad Sci USA* **96**, 7697-7704. [Paper provides evidence to support view that increased NMDA receptor function secondary to Src activation and raised

intracellular sodium may underpin physiological and pathophysiological enhancement of excitatory transmission in the dorsal horn of the spinal cord and elsewhere in the central nervous system.]

Zeilhofer H.U. (2007) Prostanoids in nociception and pain. *Biochem Pharmacol* **73**, 165-174. [Review of the role of different prostaglandins, prostaglandin synthases and prostaglandin receptors in pain pathways.]

Zhang X.F., Zhu C.Z., Thimmapaya R., Choi W.S., Honore P., Scott V.E., Kroeger PE., Sullivan J.P., Faltynek C.R., Gopalakrishnan M., Shieh C.C. (2004) Differential action potentials and firing patterns in injured and uninjured small dorsal root ganglion neurons after nerve injury. *Brain Res* **1009**, 147-158. [Electrophysiological study in isolated small dorsal root ganglion (DRG) neurons after L5/L6 spinal nerve ligation in rats indicates that tetrodotoxin (TTX)-resistant Na^+ channels play an important role in regulating action potentials and firing patterns in small DRG neurons and that downregulation in injured neurons and upregulation in uninjured neurons have differential roles in shaping electrogenesis, and perhaps pain transmission, in these neurons.]

Zhao J., Seereeram A., Nassar M.A., Levato A., Pezet S., Hathaway G., Morenilla-Palao C., Stirling C., Fitzgerald M., McMahon S.B., Rios M., Wood J.N. (2006) Nociceptor-derived brain-derived neurotrophic factor regulates acute and inflammatory but not neuropathic pain. *Mol Cell Neurosci* **31**, 539-548. [Study using Cre-loxP system to delete BDNF in most nociceptive sensory neurons in mice showed that BDNF released from nociceptors plays no role in the development of neuropathic pain but plays an important role in regulating inflammatory pain thresholds and secondary hyperalgesia.]

Zollner C., Stein C. (2007) Opioids. *Handb Exp Pharmacol* **177**, 31-63. [Review of opioid receptor pharmacology and signalling, as well clinical use of opioid analgesics and their adverse event profiles.]

Biographical Sketches

Professor Maree T. Smith was born in Brisbane and educated at The University of Queensland, Brisbane, Queensland, Australia. Profesor Smith graduated with a Bachelor of Pharmacy in 1975 followed by B Pharm (Hons) in 1976 and PhD in Medicine in 1983.

Since 2005, she has been employed as the Director of the Centre for Integrated Preclinical Drug Development and she has a joint appointment (20%) as Professor of Pharmacy at The University of Queensland, Brisbane, Queensland, Australia. Her previous appointments include Professor of Pharmacy (2004), Reader in Pharmacy (1999-2003), Senior Lecturer in Pharmacy (1995-1998) and Lecturer in Pharmacy (mid 1989-1994) at The University of Queensland, Brisbane, Queensland, Australia. Prior to that (1984-mid-1989), she undertook postdoctoral training in pain medicine with Professor Tess Cramond in the Division of Anaesthetics, The University of Queensland, and in bioanalytical methods, pharmacokinetics and pharmacokinetic modeling in the Department of Medicine, The University of Queenland. She is a member of the editorial board for Pain: Clinical Updates.

Professor Smith is a member of the International Association for the Study of Pain, Pharmaceutical Society of Australia, Australian Pain Society, Australian Society for Medical Research, Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, Australasian Pharmaceutical Sciences Association, Women in Biotechnology and AusBiotech.

Dr Samantha South was born in Brisbane and educated at The University of Western Australia, Perth, Western Australia and The University of Queensland, Brisbane, Queensland, Australia. Dr South graduated with a Bachelor of Pharmacology from The University of Western Australia in 1994, moved to Queensland the following year and completed a Postgraduate Honours degree in Pharmacology in 1995 followed by a PhD in Pharmacy in 2000.

Since 2005, Dr South has been employed as the Technical and Quality Control Manager for the Efficacy laboratory of the Centre for Integrated Preclinical Drug Development and she has a joint appointment (10%) as a Senior Research Officer within the School of Pharmacy at The University of Queensland, Brisbane, Queensland, Australia. Her previous appointments include Senior Research Officer, School of Pharmacy at The University of Queensland (2004-2005), Senior Research Fellow, The Garvan Institute, Sydney, New South Wales, Australia (2003-2004) and Senior Resarch Officer, The Weill Medical College of Cornell University, New York, New York, USA (1999-2003).

Dr South is a member of the International Association for the Study of Pain, the Australian Pain Society, Australian Society for Medical Research and Women in Biotechnology.