

Tackling the burden of pain

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Abstract

Pain is an almost universal human experience that is essential for survival. Nevertheless, pain is also a deeply, intensely personal event. Patients with a congenital inability to perceive pain can walk over burning coals, stab knives through their arms and drive spikes through their hands. Some patients with congenital limb abnormalities endure phantom pain in an arm or leg they have never had. The wide range of currently available analgesics allows nurse prescribers to tailor treatment to each patient. For example, as paracetamol acts through a different mechanism to codeine, combination therapy increases the proportion of patients that experience adequate analgesia. This feature examines the neurological basis of pain and reviews the role of co-codamol.

Pain is, simultaneously, a universal human experience and deeply, intensely personal. Almost everyone agrees that hitting their thumb with a hammer hurts. However, the severity of pain each of us perceives and our response varies. Two extreme examples make the point: patients born with a congenital inability to perceive pain can walk over burning coals, stab knives through their arms and drive spikes through their hands without flinching (Drenth and Waxman, 2007). In contrast, some patients with congenital limb abnormalities can endure phantom pain in an arm or leg that they were born without (Senok and Nayar, 2006).

Nevertheless, we would soon die without pain. Pain allows us to identify and locate a potentially hazardous stimulus. The discomfort triggers withdrawal reflexes and behaviours that reduce or prevent tissue injury. Pain inhibits movement of the damaged area, which aids wound healing. Pain's cognitive, motivational and emotional elements modify behaviour to prevent future damage (Vadivelu et al, 2009). You should only burn your fingers once. Unfortunately, chronic pain's cognitive and emotional elements can become dysfunctional and maladaptive. Chronic pain sufferers are four times more likely than controls to suffer

depression or anxiety, for example (Brennan et al, 2007). Occasionally, chronic pain 'destroys the will to live' (Gilson et al, 2007).

The neurology of pain

Pain's subjective and emotional elements make defining the experience difficult. Clinically, if a patient says a part of their body hurts, you need to take their report at face value, even if there is no obvious cause. However, such definitions are not particularly useful for research. So, many researchers cite the International Association for the Study of Pain's (IASP's) definition of pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. In other words, 'pain is that experience we associate with actual or potential tissue damage' (IASP, 2009).

Peripheral nerves convey local signals associated with tissue damage (such as inflammation or stimulation of pain receptors) to the central nervous system. Myelinated A δ nerves and unmyelinated C fibres carry fast (sharp, stinging) and slow (dull) pain signals respectively. The pain signals conveyed by myelinated A δ nerves move at between 5 and 25 metres per second. So, these signals take less than a second to alert the person to the injury, localise the source and trigger reflex withdrawal responses. C fibres are slower: the signal moves at less than 2 metres a second. As a result, C fibres take several seconds or even minutes to conduct the signal. Patients often perceive pain transmitted by C fibres as a diffuse burning or a stabbing sensation (Vadivelu et al, 2009).

Gate Control Theory

According to the 'Gate Control Theory of Pain', the spinal cord integrates pain signals with inputs from sensory nerves. Essentially, the theory suggests that the intensity of the pain signal that moves up the spinal cord to the brain depends on the balance between the activity of large myelinated mechanoreceptive fibres (A- α and A- β fibres)—which respond to pressure, movement and vibration—and the A δ and C nerves. Increasing the activity of A δ and C nerves tends to increase pain, i.e. 'opens the gate'. Increasing the activity of A- α and A- β fibres tends to reduce pain, i.e. 'closes the gate' (Senok and Nayar, 2006). That's why rubbing a sore area may alleviate

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mild pain. Analgesics close the gate either by reducing the strength of the pain signal, either in the central nervous system (CNS) (opioids) or in the periphery (non-steroidal anti-inflammatories; NSAIDs).

The Gate Control Theory of Pain proved highly influential in physiologists' understanding of nociception. Indeed, the theory accounts for many aspects of acute pain. However, the Gate Control of Theory of Pain is less successful when applied to chronic pain. How could, for example, the Gate Control theory account for phantom pain? Such deficiencies promoted the development of alternative explanations. One of the most interesting suggests that the CNS contains a 'self-image' drawn by the interaction between our genes and our accumulated sensory experiences. Normally, the brain instigates an appropriate measured response when a pain signal arrives and 'threatens' the integrity of the self-image. However, in some cases the 'program' embedded in the self-image triggers inappropriately, resulting in chronic, pathological pain conditions. So in patients who experience phantom pain the self-image retains or is genetically programmed with the limb's location (Senok and Nayar, 2006).

Closing the gate

According to the classic theory, analgesics close the 'pain gate'. For example, inflammatory signals, such as chemical messengers (cytokines) released by

white blood cells, increase the production of several prostaglandins (PGs) linked to pain, inflammation and fever (Süleyman et al, 2007). For example, PGE_2 and PGI_2 augment the pain-inducing effects of bradykinin. PGE_2 also seems to induce peripheral hyperalgesia (increased pain) and allodynia (pain produced by normally innocuous stimuli) (Sekiguchi et al, 2008). However, certain prostaglandins (including PGE_2) inhibit the production of some proinflammatory cytokines (Calder, 2009). Pain intensity reflects, in part, the balance between these pro- and anti-inflammatory signals.

Cells make prostaglandins from a fat in cell membranes called arachidonic acid. An enzyme (phospholipase A2) releases arachidonic acid from the cell membrane. Another enzyme—cyclo-oxygenase (COX)—converts arachidonic acid into PGG_2 and, in turn, into PGH_2 . PGH_2 then undergoes further conversion into other prostaglandins (Süleyman et al, 2007). Humans express at least two types (isoforms) of COX. COX-1 is active continually (constitutive expression) and produces prostaglandins essential to maintain normal physiology. For instance, COX-1 produces the prostaglandins that protect the gastrointestinal tract—which is why non-selective NSAIDs produce gastrointestinal side-effects. Expression of COX-2 rises as part of the inflammatory response (inducible expression). Inhibiting COX-2 accounts for NSAIDs' analgesic and anti-inflammatory



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benefits (Rao and Knaus, 2008). Paracetamol may act, at least in part, by inhibiting COX-2 (Hinz et al, 2007).

If simple analgesics do not effectively control pain, nurse prescribers can move to opioids. The Sumerians, a civilization in southern Mesopotamia, used the opium poppy (*Papaver somniferum*) as an analgesic around 4000 BC. *P. somniferum* is a rich source of alkaloids, including codeine and morphine (Amabile and Bowman, 2006). Enzymes in the liver metabolize codeine to morphine. However, around 6–10% of Caucasians lack the enzyme responsible for this biotransformation and, as a result, codeine is ineffective (de Craen et al, 1996). Chemists also developed semi-synthetic and synthetic opiate agonists (Amabile and Bowman, 2006) allowing prescribers to tailor treatment to the patient.

Despite being valued as an analgesic for thousands of years, researchers only discovered endogenous opioid receptors in the CNS in 1973. Pharmacologists have since identified three endogenous chemicals that bind to these receptors: enkephalins; beta-endorphins; and dynorphin. Research also delineated three families of opioid receptors, designated mu, kappa and delta. Mu-receptors, the main family associated with analgesia (Pharo and Zhou, 2007) seem to modulate pain pathways in the brain. Delta-receptors may contribute to pain pathways in the spinal cord (Nicholson, 2007). All opioid analgesics agonize CNS mu-receptors, which modifies the sensory and emotional components of pain (Amabile and Bowman, 2006).

Several other pathways seem to contribute to the pain 'experience'. For example, N-methyl-D-aspartate

(NMDA) receptors, which mediate the actions of the neurotransmitter glutamate, in peripheral nerves and CNS contribute to acute and chronic pain. Stimulation of A-delta and C peripheral pain fibres activates and increases the number of NMDA receptors. This, in turn, leads to allodynia and hyperalgesia, which pose particular problems in patients with neuropathic pain (Pharo and Zhou, 2007).

Role of co-codamol in managing pain

In 1986, the World Health Organization (WHO) suggested that clinicians should follow a stepped approach to pain management. Initially, patients receive paracetamol or NSAIDs with or without adjuvant therapy. If these fail to control pain adequately, the prescriber adds mild to moderate opioids (such as codeine) to paracetamol. If pain persists, the clinician adds stronger opioids, such as morphine or transdermal fentanyl, and the dose titrated to produce analgesia (Pharo and Zhou, 2007).

Nurse prescribers can prescribe various strengths of co-codamol (8/500, 15/500 and 30/500 mg of codeine phosphate and paracetamol respectively), allowing the clinician to tailor the dose to the patient. As paracetamol or NSAIDs act through different mechanisms to codeine, combination therapy is logical and effective. For example, a meta-analysis of 24 studies assessed 400–1000 mg paracetamol and 10–60 mg codeine. Adding codeine to paracetamol increased analgesia by 5%. Codeine's additional efficacy when added to paracetamol was comparable to the difference in analgesia between codeine and placebo (de Craen et al, 1996).

Macleod et al (2002) compared paracetamol 1000 mg with and without codeine 30 mg following surgical removal of impacted third molars in 82 patients. The average increase in pain intensity during the 12 hours after surgery was significantly less in patients receiving paracetamol plus codeine than in those receiving paracetamol alone. Of the patients who received the paracetamol–codeine combination, 62% used additional analgesics (ibuprofen) compared with 75% of those on paracetamol alone.

A systematic review of 31 randomized, controlled trials in postoperative pain estimated numbers needed to treat (NNT) using paracetamol 1000 mg and 600/650 mg to produce at least a 50% pain reduction of 3.6 and 5.0 respectively (compared with placebo). Paracetamol 600/650 mg plus codeine 60 mg had a NNT of 3.1. In direct comparisons, adding 60 mg codeine to paracetamol resulted in 12 extra patients in every 100 achieving at least 50% pain relief. The NNT for adding codeine 60 mg was 9.1 (Moore et al, 1997).

Most side effects associated with opioids result from agonism of mu-opioid receptors in the CNS,

gastrointestinal tract and other organs. So, classic opioid side-effects include sedation, confusion, pruritus, nausea and vomiting, respiratory depression and constipation. Patients often develop tolerance to many of these adverse events including sedation, nausea and vomiting. However, patients tend not to develop tolerance to opioid-induced constipation (Amabile and Bowman, 2006).

Codeine is, of course, a mild opioid and is well tolerated by most patients. In the study of pain following molar extraction, 18% and 13% of patients who received paracetamol plus codeine and paracetamol alone respectively experienced side-effects. This difference did not reach statistical significance (Macleod et al, 2002). Quiding et al (1982) reported the results of a study that enrolled 266 patients suffering from pain after removal of an impacted lower wisdom tooth who received: paracetamol 500 mg; paracetamol 500 mg plus codeine 20 mg; paracetamol 500 mg plus codeine 30 mg; or paracetamol 500 mg plus codeine 40 mg. A dose–response emerged between the codeine dose and both analgesia and side-effects.

Conclusions

The wide range of analgesics means that there is no pharmacological reason why so many people endure pain whether it's the discomfort of a musculoskeletal injury or crippling cancer pain. The reasons for ineffective pain management run deeply into the sociology of medical practice and in our culture more widely. 'For too long, pain and its management have been prisoners of myth, irrationality, ignorance, and cultural bias,' Brennan and colleagues (2007) comment. They highlight the 'coherent position in which unreasonable failure to treat pain is poor medicine and unethical practice' (Brennan et al, 2007). It is a lesson nurse prescribers should ensure they implement in their everyday practice.

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Key Points

- Pain is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'.
- Pain signals conveyed by myelinated A δ nerves alert the person to injury, localize the source and trigger withdrawal responses. Patients often perceive pain transmitted by C fibres as a diffuse burning or a stabbing sensation.
- In 1986, the WHO suggested that clinicians should follow a stepped approach to pain management, moving up a step at a time until analgesia is adequate.
- As paracetamol or NSAIDs act through different mechanisms to codeine, combination therapy is logical and effective. Adding 60 mg codeine to paracetamol resulted in 12 extra patients in every 100 achieving at least 50% pain relief (Moore et al, 1997).
- Codeine is usually well tolerated. Nevertheless, the frequency of side-effects increased as the codeine dose rose.

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