





PAIN MATTERS

Community Information Series
Hunter Integrated Pain Service
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Medication and Persistent Pain

		Information content Intermediate
	Contacts for further discussion Your local doctor will be able to discuss medication further. Staff from Hunter Integrated Pain Service can also help if you are referred to us.	
	Links and further reading Understanding Pain (www.hnehealth.nsw.gov.au/pain /Pain information for the community/Understanding)	

Background

The human body itself produces many substances that influence the way in which “pain” messages are sent from the periphery to the brain and also the way in which the brain responds to these messages. These substances include endorphins (the body’s own morphine-like painkiller) and other chemical messengers such as noradrenalin, serotonin (5-HT) and GABA. To a certain extent we can influence the levels of these substances. Exercise, for example, increases endorphin levels. Our emotional state is linked to noradrenalin and serotonin levels in the brain. Positive emotional experiences have been shown to increase serotonin levels.

Medications (drugs) are external substances that can be used to supplement the body’s inbuilt pain killing systems. Often medications either mimic or influence the level of the body’s own painkillers. Use of medication can have the advantage of more profound pain relief (at least for a time), but this is often offset by the disadvantage of side effects. The use of morphine-like drugs can have the additional disadvantage of suppressing the body’s own endorphin levels.

In general, medications are more effective in acute pain situations. When pain becomes persistent (3 months or more) medication is less effective. A 20-30% reduction in persistent pain intensity is typical. In part this limited effectiveness relates to the mechanisms of persistent pain and in part to the problem of tolerance. Tolerance means that a drug becomes less effective over time as the body gets used to its presence.

Medication can be administered by various methods but for persistent pain the “by mouth” route is generally preferred in the first instance. When medication is started it is usually trialed for an initial 2-4 week period. At the end of the trial period, the benefit and side effects need to be weighed up before deciding about the value of maintenance therapy

Medication in persistent pain is ideally used as part of holistic, “whole person” management (see Understanding Pain). In this setting time limited maintenance therapy is often recommended (3-6 months). The aim is to provide breathing space to help the person develop other strategies with greater potential for long term gain. The medication is then tapered, ceased and reviewed at the end of the 3-6 month period. In some situations there may be value in continuing medication for a longer time. However the majority of people with persistent pain do not get significant benefit from the long term use of medication.

Types of Medication

Pain pathways are complex. Therefore multiple types of medication can bring potential benefit. At times combinations of medications from different groups can be used. The main groups to consider are the non-steroidal anti-inflammatories and paracetamol, opioids (morphine-like painkillers), antidepressants and anticonvulsants (drugs used for epilepsy).

Non-steroidal anti-inflammatory drugs and paracetamol

These drugs work by modifying the inflammatory response. Inflammation is the process by which the body heals after injury. Many chemical mediators are released around the site of injury. This causes redness, swelling and pain, but is necessary for the repair of the injured tissues. A group of inflammatory substances called prostaglandins are part of this process. Prostaglandin production is controlled by enzymes called COX-1 and COX-2. Anti-inflammatory drugs act by inhibiting the action of COX-1 and COX-2 and therefore reducing prostaglandin levels. This can reduce pain if there is a component of inflammation involved.

Unfortunately side effects are common and can be serious. The inhibition of COX-1 plays a key role in causing typical side effects. This is because the prostaglandins controlled by COX-1 are involved in maintaining healthy function of the gut and kidney. The selective COX-2 inhibitors have been developed in recent years in an attempt to reduce side effects. These newer agents do have a lower risk stomach irritation, bleeding from the gut, fluid retention and kidney problems but there are still concerns about other problems such as the risk of heart attack.

The non-selective anti-inflammatory drugs (inhibiting both COX-1 and COX-2) include aspirin, ibuprofen (Brufen, Nurofen), naproxen (Naprosyn) and indomethacin (Indocid). Selective COX-2 inhibitors include celecoxib (Celebrex) and meloxicam (Mobic).

Paracetamol, like the anti-inflammatory drugs, reduces pain and fever. However, it does not affect COX-1 or COX-2. This explains its lack of inhibition of inflammation at the site of injury and also its lack of gut and kidney side effects. Its precise mechanism of action remains unclear but it does have an effect on reducing prostaglandin levels in the pain pathways of the brain and spinal cord. Although paracetamol is safer than the anti-inflammatory group at usual doses, it is toxic to the liver in overdose.

Anti-inflammatory drugs are most commonly used in acute nociceptive (tissue damage) pain of mild to moderate severity. The role in persistent pain is more limited because inflammation is not a usual component of the process. Typically anti-inflammatory drugs are recommended only in persistent pain states such as rheumatoid arthritis in which

there is ongoing inflammation. Paracetamol can have benefit in both acute and persistent pain of mild to moderate severity. Both paracetamol and anti-inflammatory drugs can be combined with other agents such as opioids to give a multi-modal effect.

Opioids

Endorphins and related substances are the body's own morphine-like painkillers. They act on specialised sites called opioid receptors. These receptors are mainly present in the brain and spinal cord, but can be transported to peripheral tissues when inflammation is present. The opioid drugs are external substances that bind to opioid receptors mimicking the action of endorphin and its relatives. There are a number of different groups of opioid receptors. The main groups are named after the Greek letters mu, delta and kappa.

The opioid drugs are all different in the way they affect the mu, delta and kappa receptors. This means that some opioids may be more effective than others for treating specific pain mechanisms. It also means that the side effect profile varies.

Commonly used opioids include codeine, morphine, pethidine, fentanyl, oxycodone, hydromorphone, methadone and buprenorphine. There are different formulations of these drugs, some short and some long acting. Generally the long acting preparations are preferred in the treatment of persistent pain. There are sustained release forms of morphine (MS Contin, Kapanol) and oxycodone (Oxycontin). Methadone (Physeptone) is long acting because it is slowly eliminated from the body. Fentanyl (Durogesic) and buprenorphine (Norspan) are available in the form of skin patches. Tramadol (Tramal, Durotram) has some activity at opioid receptors in addition to an antidepressant like action to increase serotonin and noradrenalin levels in the brain.

Constipation is the commonest side effect with long-term opioid use. Other side effects include nausea, itch, sweating, weight gain, clouding of thought processes, drowsiness and mood change. In some cases opioids can actually increase pain by causing hyperexcitability in pain related pathways (opioid induced hyperalgesia). Use of opioids at moderate to high dose can suppress the action of the pituitary gland in the brain. This gland controls the body's endocrine function. Problems related to this can include low testosterone levels (loss of sex drive and erectile dysfunction) in men and loss of periods in women. Under activity of the thyroid and adrenal glands can also result. Tramadol can interact with certain antidepressants and other drugs to cause excessive serotonin levels in the brain (serotonin toxicity).

The development of tolerance to opioids is a common problem with long-term use. This problem can be reduced by changing to another opioid agent every 12 months or so. This is called opioid rotation.

Opioids are usually very effective in treating acute nociceptive (tissue damage) pain. They can often be helpful in treating acute neuropathic (nerve injury) pain. In managing persistent pain opioids are much less effective but there can be a role in a selected subgroup of people with either nociceptive or neuropathic pain. Generally the pain reduction achieved is much less in persistent pain and the tolerance problem means further reduction in benefit over time.

Antidepressants

Antidepressant drugs act by altering the levels of specific chemicals in the brain. Noradrenalin and serotonin are the substances primarily involved and brain levels impact both mood and pain. While both substances have an effect on mood, noradrenalin appears to be more important in pain pathways. Increased brain noradrenalin can damp down transmission of pain messages. There are a number of different types of antidepressant drugs that vary in mechanism of action. The two most commonly used groups will be discussed here. Tricyclic antidepressants (TCA) act by blocking reuptake of both noradrenalin and serotonin once they have been released at their site of action. This increases the effective levels of both substances in the brain. In contrast many of the newer antidepressants act more selectively to increase serotonin levels with minimal effect on noradrenalin. These are called selective serotonin reuptake inhibitors (SSRI's).

Commonly used TCA include amitriptyline (Tryptanol, Endep), nortryptiline (Allegron), dothiepin (Prothiaden), doxepin (Sinequan) and imipramine (Tofranil). The newer SSRI group include fluoxetine (Prozac, Lovan), sertraline (Zoloft), citalopram (Cipramil), fluvoxamine (Lovan) and paroxetine (Aropax). Venlafaxine and duloxetine are newer agents that have a mixed action on both noradrenalin and serotonin more like TCA's.

Common TCA side effects include dry mouth, blurry vision, constipation, difficulty passing urine, weight gain and drowsiness. The SSRI's are generally better tolerated. Side effects can include nausea, loss of libido, tremor, hyper-arousal and drowsiness.

TCA's can be helpful in reducing severity of pain. They appear to be more specifically effective in the treatment of neuropathic rather than nociceptive pain. Doses of TCA required to treat neuropathic pain are usually lower than those needed to treat depression. TCA's, as with all antidepressants, need to be taken regularly rather than intermittently. The time to onset of pain reduction is usually 1-2 weeks as opposed to approximately 1 month for effect on mood. They can also play a role in restoring a more normal sleep pattern. The SSRI's are generally very effective in treating depressed mood but of less help in reducing pain severity.

Anticonvulsants

Anticonvulsants are a family of drugs that reduce excessive electrical activity in the brain and thereby stop seizures. The mechanism of neuropathic pain also involves increased electrical activity. This can occur in the peripheral nerves, spinal cord and brain. Some of the drugs used to treat epilepsy can therefore also be effective in neuropathic pain. Anticonvulsants act by a number of different mechanisms to reduce the excessive electrical activity. They can block the sodium or calcium channels in nerves that are part of the electrical transmission system. Some agents increase brain levels of inhibitory messengers such as GABA. Other mechanisms are not yet completely understood.

Older agents used include sodium valproate (Epilim, Valpro), carbamazepine (Tegretol) and clonazepam (Rivotril). The newer generation includes gabapentin (Neurontin), lamotrigine (Lamictal) and pregabalin (Lyrica).

Side effects include sedation and being off balance. Some anticonvulsants can irritate the liver. Drug interactions can be a problem when combining anticonvulsants with other drugs.