CHAPTER 35

CHRONIC PAIN

"chronic pain is a disease of the brain"
Borsook et al, 2010

Chronic pain is a major health problem; the prevalence in Europe is 20% (Breivk et al, 2006). In Australia the prevalence is 20.0% for females and 17.1% for males (Blyth et al, 2001).

Services are poorly developed, even in countries with advanced health care systems such as Australia (Australian Pain Society, 2010).

Treatment/management is complex, but not impossible; and may involve doctors (pain specialists), physiotherapists and psychologists/psychiatrists. As some analgesic medicines have addictive potential, risk assessment is indicated.

Pain

Pain is "an unpleasant sensory and emotional experience associated with actual tissue damage or is described in terms of such damage" (Merskey, 1979).

An important point is immediately raised by this internationally endorsed definition: pain is (at least in part) an “emotional experience”.

At least two separate components of pain can be identified, 1) a motivational/affective component, which identifies pain as negative and something to be avoided, and 2) a sensory/discriminative component which localizes the pain and forms an appropriate response.

Acute Pain

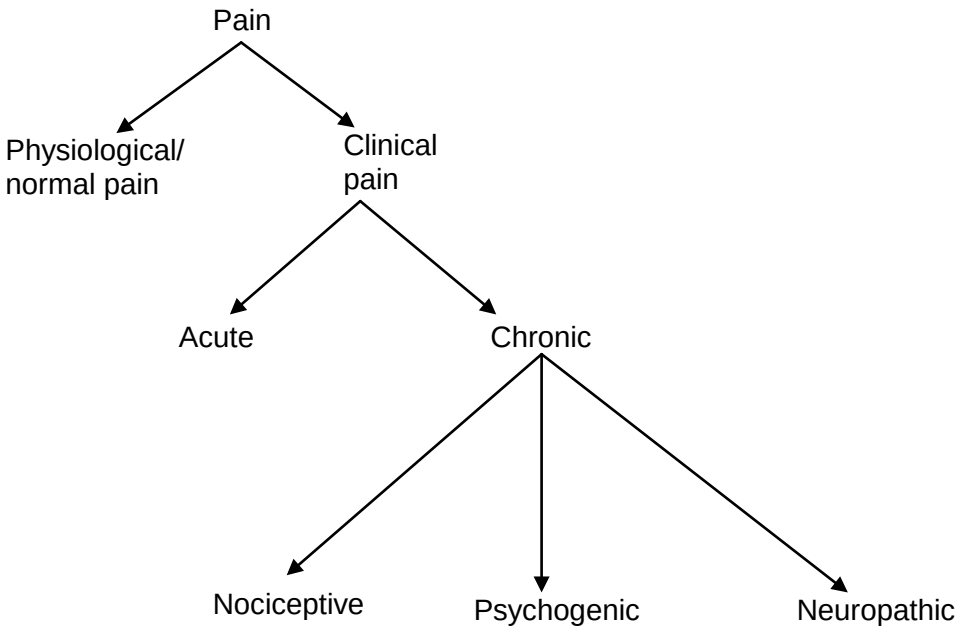
Acute pain is a warning system which halts certain actions (or inactions) and teaches us not to perform such actions (or inactions) in the future. Think of touching red hot metal. Acute pain has value in evolutionary terms.

The full details of the pain system can not be pursued in detail. However, “nociceptors” are specific primary afferent nerves which respond to potentially tissue-damaging stimuli. They pick up sensations in the skin and other organs and terminate in the dorsal horn of the spinal cord, a complex site where pathology may develop and therapy may be attempted.

Ascending fibers (second order cells) cross the cord and travel north, (predominantly) in the spinoreticular and spinothalamic tracts. The spinoreticular tract terminates in the mid brain, connecting with the periaquiductal gray matter (PAG) and other reticular structures, and (importantly) the locus coeruleus (the seat of the sympathetic system). The PAG is a major component of a descending pain inhibitory system, which impacts at the dorsal horn of the spinal cord.

The spinothalamic tract terminates at the posterior and medial thalamic nuclei (the central switching station). The thalamus (Th) projects fibers to the primary somatosensory cortex (SI; believed to provide for the localization of pain), secondary somatosensory cortex (SII; Brodmann area 40, supramarginal gyrus, at the posterior end of the lateral fissure), the anterior cingulate cortex (ACC), and the insular cortex (IC). There are also projections to the prefrontal cortex (PFC), but this region is probably less important in acute than other forms of pain (Akparian et al, 2005).

Chronic pain



A classification of pain. Adapted from Pridmore, 2002

Chronic pain is defined as pain which persists for longer than 3 months, or past the usual healing time. This definition is not without difficulties. It applies particularly well to post injury pain. [Discussed in greater detail below.]

Nociceptive pain can take a chronic form. The pain of rheumatoid arthritis (for example) persists beyond 3 months. While such pain can be classed as "chronic", there is ongoing inflammation, and such conditions can be considered "chronic nociceptive pain".

Psychogenic pain has been described as pain which arises from the emotional life of the individual, in the absence of any physical pathology. In the current era, such pain (in the complete absence of physical pathology) is very rarely encountered. However, mental disorders make physical pain more difficult to tolerate. There is also potential for circularity: pain can caused emotional distress, which in turn, makes pain worse.

Neuropathic pain is caused by a "lesion or dysfunction of the nervous system" (Merskey & Bogduk, 1994). A lesion of a peripheral nerve by trauma or herpes zoster (for example) may result in various mechanisms which contribute to **chronic pain**.

Peripheral sensitization: describes changes in damaged peripheral nerves, including painful spontaneous firing and abnormal excitability.

Central sensitization: describes changes in the spinal cord, and supra spinal structures which are associated with **chronic pain**.

Loss or dysfunction of peripheral nerves leads to dysfunction of the second order ascending cells of the spinothalamic tract (for example).

When an insulted peripheral nerve survives in damaged form, increased (spontaneous) firing may lead to changes and dysfunction in second order cells. When an insulted peripheral nerve dies, there is a loss of afferent input, leading to "deafferent hypersensitivity" in second order cells. Also, when an insulted peripheral nerve dies, reorganization in the dorsal horn may lead to second order neurons linking up with the "wrong" peripheral nerves, such that innocuous peripheral sensations are presented to the brain as pain input. This greatly increases the amount of pain information reaching the brain, and a gentle breeze on the skin (for example) may cause pain. In addition, reorganization may involve the sympathetic nervous system, and activity in this system (e.g., constricting a blood vessel) may trigger pain.

Dysesthesia and allodynia are clinical signs which are pathognomonic of neuropathic pain and have both peripheral and central sensitization components. **Dysesthesia** is abnormal spontaneous sensations such a sudden "electric shocks" and "pins and needles". **Allodynia** is abnormal sensation in response to external stimuli, such as extreme pain in response to innocuous touch (e.g., when a sleeve touches a neuropathic hand).

Chronic pain is a difficult term. Clearly, rheumatoid arthritis (for example) is associated with **chronic pain**, but if this can be controlled in the rheumatology clinic and the patient lives a satisfying life, the term has less relevance. The term **chronic pain** is used particularly following trauma or degeneration, and pain continues beyond the normal healing time, e.g., when there is persistent pain from healed herpes zoster lesions or persistent phantom pain following amputation. The term **chronic pain** is also used for chronic back pain, especially chronic back pain with minimal imaging findings.

The characteristic of **chronic pain** is "**suffering**", by which is meant, there is not only pain, but a pervasive experience of distress. There is a loss of the ability to work or perform normal daily functions. There is inactivity, loss of social life and energy, low mood and high anxiety. There may be difficulty with concentration and reduced ability to solve problems.

Nociceptive and neuropathic pain frequently coexist. Even when an injury/degeneration has not damaged peripheral nerves**, the pain experience may alter the central nervous system**. This has led to the increasingly endorsed theory that "**chronic pain** is a disease of the brain" (Borsook et al, 2010).

Transition from acute to chronic pain is not well understood, but includes brain changes [next section]. The importance of the interaction of the nervous and **immune system**s in this process is now receiving attention (Mifflin & Kerr, 2013).

Brian changes in chronic pain

Brain changes associated with **chronic pain** have only been identified in recent times, and are a currently being excitedly explored. Much remains to be discovered.

These changes, discussed in terms of “neuroplasticity”, and “central reorganization”, have lead to “central sensitization” (e.g., light pressure is experienced as painful pressure). They may occur in the absence of obvious peripheral nerve damage, but are nevertheless termed “neuropathic” changes.

Loss of gray and white matter and alterations of brain function have been described. The nature of the loss of gray matter remains uncertain; it may represent loss or atrophy of nerve cells, dendrites, synapses, or glia. Grachev et al (2001) suggested “neuronal loss and degeneration”, however, Rodriguez-Raecke et al (2009) found that much of the cerebral gray matter lost in association with the **chronic pain** of OA hip was restored after successful hip replacement, suggesting that actual loss (death) of cells may not be the explanation.

As described above, acute pain is associated with activity in SI, SII, ACC, IC, Th and PFC.

However, **chronic pain**, gray matter loss and increased activity is most commonly found in the PFC, suggesting a greater role for this region (Akparian et al, 2005). A host of other studies support this finding, and are listed in the next section. Thus, acute (experimental) and **chronic pain** are underpinned by overlapping, but slightly different, brain maps.

The prominent activation of the PFC (and projection areas) and the demonstrated a disruption of the functional connectivity between brain regions (Baliki et al 2008) are the probable explanation for chronic pain patients experiencing, in addition to pain, depression and anxiety, sleep disturbance and decision-making (cognitive) abnormalities.

Increased activity is also frequently demonstrated in the PAG (Gwilym et al, 2009**)** and the cerebellum. The PAG is an important component of the descending pain inhibition system, but the role of the cerebellum in **chronic pain** is unknown.

There are similarities in the brain maps of individuals with the same **chronic pain** condition. However, overlap between the maps of different disorders, makes uncertain whether a distinct brain map will be discovered for each **chronic pain** disorder.

Imaging studies in chronic pain

1. In irritable bowel syndrome (IBS), PET demonstrated pain associated with rectal distention is associated with increased activity in the frontopolar region (Brodmann area 10; parts of the superior and middle frontal gyrus) and no activity in ACC. The reverse is the case in healthy individuals (Silverman et al, 1997).
2. In IBS, MRI demonstrated gray matter density changes (increases and decreases) in regions associated with depression, anxiety and cognition (Seminowicz et al, 2010).

3. In chronic back pain (CBP), magnetoencephalogam (MEG; which measures electrical activity) shows that the area of SI devoted to the back is enlarged and shifted medially (Flor et al, 1997; indicating "cortical reorganization").
4. In CBP, magnetic resonance spectroscopy (MRS; which quantifies chemical levels) shows that the N-acetyl aspartate (NAA) and glucose levels are elevated in the dorsolateral PFC, while glucose is reduced in Th (Grachev et al, 2000). MRS findings are independent of the cognitive level at the time, thus these chemical changes reflect long-term plastic modifications.
5. In CBP, MRI demonstrates a 5-11% reduction in neocortical gray matter volume (Apkarian et al, 2004). This is equivalent to 10-20 years of normal aging, and represents 1.3 cubic cm loss of gray matter for every year of chronic pain.
6. In CBP, fMRI demonstrates a disruption of the functional connectivity between brain regions (Baliki et al 2008).
7. In OA hip (in patients with increased sensitivity and referred pain), fMRI demonstrates increased activity in ACC, DLPFC and PAG (among others, Gwilym et al, 2009).
8. In OA hip, MRI shows reduced gray matter density in ACC, DLPFC, IC, and brain stem (along with some other areas). When the nociceptive focus is removed by hip replacement surgery (the only form of chronic pain which can be so "cured") there is increase in the density of most regions (Rodriguez-Raecke et al, 2009**)**.
9. In headache, MRI shows reduced gray matter density in brain regions known to be part of the pain system, similar to those of chronic pain in general (but including the hypothalamus), and these "structural changes are not headache specific" (May, 2009).
10. In persistent idiopathic facial pain, MRI demonstrates decreased gray matter volume in the ACC, IC, SI (among others), that is, in brain regions known to be part of the pain system (Schmidt-Wilcke et al, 2010).
11. In fibromyalgia, MRI reveals decreased gray matter volume in PFC, ACC and amygdale (Burgmer et al, 2009). Other studies have demonstrated abnormalities in opioid receptors and binding, blood flow, and white matter tracts (Nabel and Gracely, 2009). Older patients with fibromyalgia show decreased gray matter accompanied by compromised white matter integrity, and younger patients showed gray matter increases (basal ganglia and insula) – suggesting brain structure and function shifting from adaptive to maladaptive in older patients (Ceko et al, 2013).
12. In trigeminal neuralgia an MRI study of the people experiencing frequent trigeminal neuralgia confirmed gray matter loss confirmed in the frontal lobes, including the anterior cingulate cortex, but also the parahippocampus, temporal lobe and some other structures (Obermann et al, 2013).
13. In CBP an MRI study found significant white matter hyperintensities in the following left hemisphere tracts: anterior thalamic radiation, lower cingulate, inferior longitudinal fasciculus, superior longitudinal fasciculus and superior longitudinal fasciculus to the temporal lobe (Buckalew et al, 2013).

Cellular and chemical changes

The cellular and chemical changes of **chronic pain** are complex and remain to be clarified. It is not appropriate to cover the speculation in detail (which is a relief).

Nerve injury may cause cell membrane changes, including altered sodium, calcium and perhaps other channels, which contribute to membrane instability and painful depolarization (either spontaneously, or in response to mild stimulation). Nerve injury may also result in there dendritic sprouting and aberrant synaptic formation in the dorsal horn, such that innocuous peripheral stimuli are sent to the brain as pain information. And, connections may form between sympathetic system and pain system nerves.

The decrease in gray matter volume or density may be explained by loss or atrophy of nerve cells, dendrites, synapses, or supporting cells.

A role for the neuroglia in **chronic pain** has been proposed (Graeber and Streit, 2010).

Changes in opioid, dopamine and NMDA receptors and neurotransmitters, brain chemical concentrations (NAA), prostaglandins, and various peptides (Seybold, 2009) have been described.

Psychosocial factors

The nervous (in particular, the limbic and autonomic components), endocrine and immune systems are intimately connected and respond to environmental events; see Chapter 34, Psychoneuroimmunology.

For a discussion of somatization (the propensity of a patient to experience and report physical symptoms that have no pathophysiological explanation, to misattribute them to disease, and to seek medical attention for them) see chapter 22, Somatization. The same process applies when only minor physical abnormalities are present or suspected.

The biopsychosocial model has been given a structural underpinning. Rome and Rome (2000) speculate that disturbing early life experiences lead to plastic brain changes which predispose the individual to pain, by sensitization of corticolimbic structures.

A ‘pain-prone disorder’ has been described (Blumer and Heilbronn, 1982) in which hard working people with limited capacity to express emotions (alexithymia), after loss or disappointment, with or without painful injury of ailment, become anergic and suffer continuous pain.

It has been proposed that some hard working individuals with limited coping strategies may be able to cope and achieve a sense of self-worth and status (within their family and community) through their work, but when injury interrupts their ability to work (their

role), with few other coping skills, they easily become dependent and subject to chronic pain.

Muscle tension increases with both anxiety and pain, and exacerbates pain. Apprehension about the future exacerbates pain.

Anger exacerbates pain. The 'pain management system' which involves multiple medical consultations and delays (and in compensatable cases, multiple legal consultations, delays and court appearances) causes frustration and may exacerbate pain (Walker et al, 1999). However, it must also be considered that people predisposed to pain may also be predisposed to anger.

Dissatisfaction with support from colleagues and work supervisors is associated with the emergence of chronic pain (Macfarlane et al, 2000).

Cultural factors are important. For example, Asians living in Britain are twice as likely as Europeans to consult the general practitioner (Balarajan et al, 1989) and they commonly present with musculoskeletal pain. This may be related to relative social disadvantage, but there are clear cultural differences in the ways of responding to symptoms.

Chronic pain is more common in situations of social disadvantage, unemployment and poverty.

Assessment of chronic pain

Chronic pain is considered a disease with many symptoms (not just pain). In pain management units, assessment involves a doctor (pain specialist), a physiotherapist and a psychologist/psychiatrist. But, excellent results can be obtained by a single practitioner with a biopsychosocial mind-set.

An assessment approach to low back pain was developed using red and yellow flags. The flags approach is now being applied in **chronic pain** more generally.

Red flags indicate possible serious pathology. They indicate the need for further investigation and possibly, specialist referral.

Possible fracture	**Possible tumor/infection**	**Possible significant neurological deficit**
* Major trauma * Minor trauma in elderly of osteoporotic patient	* Age <20 or >50 yrs * History of cancer * Constitutional symptoms (fever, chills, weight loss) * Recent bacterial infection * IV drug use * Immunosuppression * Pain worse at night or when supine	* Severe or progressive sensory alteration or weakness * Bladder or bowl dysfunction * On examination: evidence of neurological deficit

Yellow flags are psychosocial indicators suggesting increased risk of progression to long-term distress, disability and drug misuse. They include the patient's attitudes and beliefs, emotions, behaviors, family and workplace.

- The belief that pain is harmful or severely disabling
- Fear-avoidance behavior (avoiding activity because of the fear of pain)
- Low mood and social withdrawal
- Expectation that passive treatment rather than active participation is the preferred course of action

The symptoms of this disease may include pain, anxiety, depression and cognitive difficulties. Patients unable to perform their usual functions at work and home, will likely experience loss of income and self-esteem. There may be loss of energy, disinclination to activity.

Depressive and anxiety disorders are frequently described as co-morbid conditions. Even when the full diagnostic criteria for anxiety and depressive disorder are not met, some emotional symptoms are frequently present.

Until recently, emotional symptoms (anxiety, depression) were conceptualized as secondary to the disability, loss of autonomy, and the frustration of constant pain. Recent studies, however, suggest the emotional symptoms may also have a strong biological component (that the pain and the depression are the result of the same or similar cerebral events).

Chronic pain patients, understandably, want a "cure". They consult various surgeons and seek interventional approaches. As much of the problem lies in the CNS, repeated procedures will worsen rather than improve the situation. A patient who believes intervention will "cure" the pain will not be responsive to conservative (state of the art) management which emphasizes acceptance of some pain and active self-management.

Inactivity in **chronic pain** is a response to 1) avoiding movement as a means to avoiding pain, 2) **the mistaken view that pain experienced on movement means that movement will further damage the body**. However, inactivity is deleterious, leading to weakness of muscles and stiffness of joints, which leads to further pain, and further inactivity.

Nociceptive foci. As part of the physical assessment all appropriate blood and imaging tests will be performed. It may be possible (but this is not often the case) to locate a nociceptive focus i.e., degeneration of facet joints, or complex regional pain syndrome (CRPS). This chapter deals with **chronic pain** as a disease entity, and assumes that appropriate treatment of any nonciceptive focus has been provided.

Chronic pain management

When a specific nociceptive focus has been identified, a specialist procedure may be indicated. However, usually, the following approach should also be offered, as success with a specialist procedures does not have guaranteed or permanent effects, and the major burden of **chronic pain** disease remains.

Where there is significant anxiety or mood disorder, this should be treated using a verbal therapy and, if necessary, medication. (Antidepressants with a noradrenaline action [TCAs, duloxetine, venlafaxine] have the added advantage of an analgesic effect.)

Where social problems exist, these need to be addressed by social workers or others, as stressful problems worsen the pain experience.

Where alcohol and drug problems exist, these need to be addressed. The assistance of appropriate local services may be necessary.

Help the patient understand that a "cure" is unlikely, but that with advice and effort, pain can be minimized, and a more active and satisfying life can be achieved.

Help the patient understand that in **chronic pain conditions, pain associated with movement does not indicate further injury is being done.**

Help the patient understand that inactivity will make the condition worse. Encourage a return to normal function. **The involvement of a physiotherapist is indicated**. Specific exercises and gradual return to normal activities (perhaps with some limitations) are recommended (van Middelkoop et al, 2010).

Teach the patient **"pacing"**: large jobs (such as the family ironing) to be broken down into a series of smaller tasks, and excessive amounts should not be performed at any one time. This especially applies when patients have 'good' days, when they are relatively pain free and are tempted to 'make hay while the sun shines'. Excessive activity leads to "flare ups" (exacerbation) of symptoms. Temporary exacerbations of pain are temporarily disabling and permanently discouraging.

Cognitive behavior therapy (CBT) is helpful in the management of emotional difficulties (including anxiety and depression) and this setting provides an educational opportunity. **Involvement of a psychologist** in the treatment of **chronic pain** is indicated (Eccleston et al, 2009).

Medication in chronic pain

"The desire to take medicine is perhaps the greatest feature which distinguishes man from the animals.' Sir William Osler, 1904

The aim of pharmacological management of chronic pain is not to completely remove, but to reduce pain. Complete removal is not possible. (Of course, complete removal might be achieved with a strong analgesic and a trivial acute pain.) The expectation of complete removal of chronic pain using pharmacological agents leads clinician and patient down a dark track. Most patients are satisfied with a 30% reduction in pain (some are not, of course). Nevertheless, a greater than 50% reduction of chronic pain using pharmacological agents is rarely achieved.

Medication should be used in conjunction with non-pharmacological (education, psychotherapy, exercise and activity) measures.

Simple analgesics

Commence with simple analgesics. If stronger analgesics are required later, the simple analgesics should be retained as they reduce the amount of stronger analgesics then required ("opioid sparing effect").

Paracetamol is usually well tolerated by the gut (in contrast to aspirin) but causes severe liver disease in overdose. Can be taken qid, to a maximum of 4000 mg per day.

Combination simple analgesics

These agents have little role in **chronic pain**, but may be used in the elderly who are less tolerant of stronger agents.

Non-steroidal anti-inflammatory agents

These agents are not appropriate for long-term use in **chronic pain**, because of gastrointestinal, kidney and other potential complications. This is a bold statement (by a timid writer). A recent metal-analysis (Chung et al, 2013) "endorses the use of COX-2 NSAIDs as the first line drug for chronic nonspecific low back pain".

To which Mark Twain may have muttered, "Lies, damned lies and statistics".

Antidepressants

Tricyclic antidepressants (TCAs) and some more recent antidepressants (venlafaxine, duloxetine, milnacipran; Bernstein et al, 2013) have an important role in **chronic pain** management, which is independent of their antidepressant action. Their norepinephrine and serotinergic actions increase inhibition in the dorsal horn. The side effects differ somewhat from one agent to another; the TCAs being dangerous in overdose, but all have some anticholinergic actions, and the potential for sedation.

Antidepressants have been identified as first line drugs in neuropathic pain, (Sindrup and Jensen, 2000), and usefully effective in low back pain, osteoarthritis, rheumatoid arthritis, fibromyalgia (Fishbain 2000) and postherpetic neuralgia (Kanazi et al, 2000).

Analgesic effects are commonly encountered at lower than the usual antidepressant dose.

Amitriptyline, commence at 10-25 mg per day (best given at night); for analgesic effects the dose can be increased to 100 mg per day, for antidepressant effects the maximum is 300 mg per day.

Anticonvulsants

The anticonvulsants are a group of unrelated drugs with a range of actions (including effects on the stability of membrane channels, NMDA receptors and GABA activity). Thus, they have various adverse effects including GI upset, rash, lethargy, nausea and ataxia. GI upset may be managed by taking with food, rash may be avoided by starting with low doses, many other adverse effects are dose related. Rare life-threatening idiosyncratic reactions appear to be limited to carbamazapine and sodium valproate (agranulocytosis, Stevens-Johnson syndrome, aplastic anemia, thrombocytopenia, hepatic failure, dermatitis, serum sickness and pancreatitis).

Carbamazapine has been used for decades in the treatment of neuropathic pain (in particular, trigeminal neuralgia). Also, headache prophylaxis. Controlled release tablets are taken bd, starting at 200-400 mg per day (or less), with a daily maximum of 1200 mg.

Sodium valproate has been mainly used in neuropathic pain and headache prophylaxis. It has been associated with hair thinning, which was believed to be prevented by zinc supplements (recently questioned). Begin at 200 mg bd, gradually increase, guided by effect and side effects. The maximum is 2500 mg per day.

Gabapentin, a GABA analogue, is effective in a range of neuropathic conditions. An advantage being, it is generally well tolerated (as well as reducing anxiety and improving sleep). A disadvantage is that this drug is expensive. Recently, this drug has been used as a more general analgesic, where there is no clear evidence of nerve damage (e.g., non-specific back pain). In such cases, the assumption is made that nerve damage is present but not demonstrable. Begin with using 300 mg tablets, 1 on day 1, 2 (spaced) on day 2, 3 (spaced) on day 3, to a maximum of 2400 mg per day.

Pregabalin is effective in the treatment of neuropathic pain. It has the distinction of being approved by the FDA for the treatment of fibromyalgia (the only other drug approved for this condition being duloxetine) and anxiety. The added distinction is that the manufacturer, Pfizer, pleaded guilty to misbranding “with the intent to defraud or mislead”. Be that as it may, clinical experience is that pregabalin is an effective analgesic. One open study (Toth, 2010) suggests pregabalin may have advantages over gabapentin, but this yet to be proven. Pregabalin is even more expensive that gabapentin and at the moment, is only available in most countries under special circumstance. A product to watch.

Opioids

The aim of pharmacological management of chronic pain is not to completely remove, but reduce pain. A greater than 50% reduction of chronic pain using opioids is rarely achieved.

Chapter 13, "Substance Use Disorders", contains useful information

All opioids have adverse effects, which are too numerous to list here, but involve the neurological, cardiopulmonary, gastrointestinal, urinary, endocrine and immune systems. Hyperalgesia (increasing pain) can be difficult to diagnoses.

[An interesting proposal by Stein & Baerwald (2013) is to develop a method of augmenting the effects of endogenous opioids by inhibiting their degrading enzymes.]

Remain alert to aberrant drug taking behavior: taking medication other than as prescribed, dropping drugs down the toilet, lost scripts, consulting other doctors, injecting oral preparations, selling.

All opioids should be commenced on a "trial" basis and reviewed after 1 month. If there has not been and improvement in function, opioids should be ceased. A trial is necessary because not all pain is opioid sensitive, and it is unethical to prescribe a potentially harmful drug which is providing no functional benefit.

Long acting drugs are preferred in chronic pain. Maximum doses are listed below.

If the maximum dose has been achieved, additional short acting drug for "break through" pain, must not be provided.

Recommendation: before commencing opioids, the case should be discussed with a specialist.

Codeine 30mg plus aspirin/paracetamol is short acting and is not well suited as the regular treatment in **chronic pain**. However, this has a place when prn medication is sufficient, or as a "breakthrough" treatment.

Tramadol causes nausea and should not be used in combination with antidepressants (because serotonin action may contribute to the serotonin syndrome, delirium, etc). Regular preparation, maximum daily dose, 300mg; slow release preparation, maximum daily dose, 400mg.

The meta-analysis mentioned above (Chung et al, 2013) found, "Tramadol shows no statistically significant effect on pain relief, but has small effect sizes in improving function". Replication is awaited.

Oxycodone hydrochloride, is short acting and can be used in combination with longer acting opioids for breakthrough pain. 5 mg tablet (Endone; equivalent to 7.5 mg morphine) to be used a maximum of once per day. If 5 mg is being used daily, consider adjusting the long acting drug. However, do not exceed the limit of 120 mg of morphine equivalent per day.

Preferred long acting opioids

Morphine, maximum dose 120 mg per day (MS Contin, Kapanol, 60 mg bd).

Oxycodone, maximum dose 80 mg per day (Oxycontin, 40 mg bd)

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