CHAPTER 35

CHRONIC PAIN

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

"You gotta be kidding! Your back *still* hurts?!"

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 in many countries, even in some of those 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. While medical cannabis is popular, supporting evidence is not strong. Transcranial magnetic stimulation is under investigation.

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”.

A related (rather difficult) concept - 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

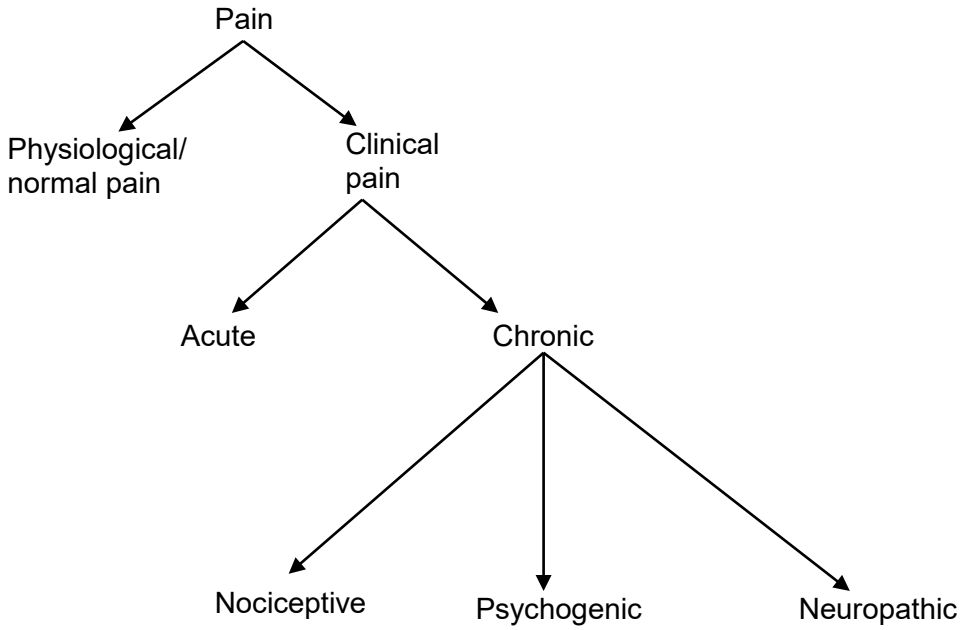
Acute pain is a warning system which halts certain actions (or inactions) and teaches us not to perform such actions (or inactions) in the future. Think of touching red hot metal. Acute pain has value in evolutionary terms.

“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 midbrain, 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 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, and the insular cortex. There are also projections to the prefrontal cortex, but this region is probably less important in acute and more important in 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 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 (psychosocial circumstances) of the individual, in the absence of physical pathology.

The DSM-5 describes **somatic symptom disorders** – a mental disorder which manifests as physical symptoms suggesting illness or injury, but which cannot be explained by the medical condition (see Chapter 22) – psychogenic pain fits with somatic symptom disorders.

Mental disorders make physical pain more difficult to tolerate. And, there is potential circularity: pain can causing 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 supraspinal structures which are associated with **chronic pain**.

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).

Suffering - a characteristic of **chronic pain** - by **suffering** 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 and some interaction of the nervous and **immune systems** (Mifflin & Kerr, 2013).

Brian changes in chronic pain

Brain changes associated with **chronic pain** are being excitedly elucidated.

They are discussed using the terms of "neuroplasticity", and "central reorganization", have led to "central sensitization".

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. 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 primary somatosensory cortex, secondary somatosensory cortex, anterior cingulate cortex, insular cortex, thalamus and prefrontal cortex.

The prominent activation of the PFC and the demonstrated 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.

Examples of imaging studies in chronic pain (Not to be memorized)

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 - 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**)**.

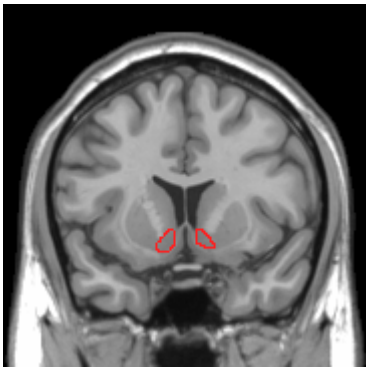
9. Headache - MRI shows reduced gray matter density in brain regions known to be part of the pain system, similar to those of chronic pain in general (but including the hypothalamus), and these "structural changes are not headache specific" (May, 2009).
10. Idiopathic facial pain - MRI demonstrates decreased 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. 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. Trigeminal neuralgia - MRI study of 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. CBP - 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 in chronic pain
- remain to be clarified.

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 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.

Cellular and chemical changes in chronic pain with depression

A probable role for the nucleus accumbens (NAc) (located in the basal forebrain between the caudate and the putamen) had been described for chronic pain with depression (Massaly et al, 2019). The NAc contains neurons with kappa opioid receptors (KOP). It is proposed that pain causes neuronal release of dynorphin (an opioid peptide) which stimulates KORs which leads to a reduction in certain neurotransmitter release which causes depressive symptoms.


Nucleus accumbens (NAc)

Letzen et al (2019) also studied pain with depression – they examined functional connectivity (FC) and concluded mesocorticolimbic dysfunction played a role in depression. [The mesolimbic pathway includes the ventral striatum, which includes the NAc.]

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).

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

Anger exacerbates pain. The 'pain management system' involving multiple medical consultations and delays (and in compensated cases, repeated 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) - commonly presenting with musculoskeletal pain. This may be related to relative social disadvantage, but there are clear cultural differences in the ways of responding to symptoms. In the USA, Native Americans have a higher prevalence of chronic pain that any other racial/ethnic group (Rhudy et al (2019).

A possible predisposed group – it is 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 (unable to perform their role), with few other coping skills, they easily become dependent and subject to chronic pain. This topic: under construction.

Bass and Yates (2019) have emphasized the importance of psychosocial factors in chronic pain and complain about the lack of psychiatrists in pain clinics in the UK.

Assessment of chronic pain

Chronic pain has been designated 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.

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 management

Chronic pain patients, understandably, want/seek a "cure". They consult various 'experts' and welcome 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 is often responsive to state of the art conservative management which emphasizes acceptance of some pain and the need for active self-management.

Inactivity in **chronic pain** is a logical: 1) avoiding movement is a means to avoiding pain, and 2) **it makes sense that if movement causes some pain, it must be causing further damage the body**. However, some pain on movement does NOT indicate further body damage, and inactivity is deleterious, as it leads to weakness of muscles and stiffness of joints, which results in further pain, and further inactivity.

When a specific nociceptive focus has been identified, a specialist procedure may be indicated. However, usually, the approach described in these paragraphs should also be offered, as success with interventional procedures is neither guaranteed nor permanent, 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 also, this setting provides an educational opportunity. However, there is little evidence that CBT reduces pain or increases activity. McNaughton et al (2019) studied 471 patients with chronic pain treated with CBT - for some the pain was medically explained and for others there was no medical explanation. There was no significant improvement in pain for either group.

Mindfulness-based therapy is frequently reported to be effective in chronic pain – and eases emotional distress. However, Jackson et al (2019) examined 2818 studies of the effects of mindfulness therapy on the physical function of people suffering from chronic pain - they found no convincing evidence of improvement of physical function.

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. 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.

<u>Simple analgesics</u>
Start here. 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; 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, plead guilty to misbranding "with the intent to defraud or mislead". Be that as it may, clinical experience is that pregabalin is an effective analgesic.

Evidence has emerged of a pregabalin euphoric effect (Crossin et al, 2019) which suggests potential for abuse. Whether this applies to gabapentin is uncertain.

Opioids

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

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 been no improvement in function, opioids should be ceased. 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.

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

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

A national cohort study of tramadol users in Norway (Birke et al, 2019) found worrying evidence of problematic use.

Oxycodone hydrochloride, is short acting and has been used in combination with longer acting opioids for breakthrough pain. A recent review states, "Oxycodone possesses pharmacologic qualities that render it disproportionately liable to abuse and addiction and the risks of any long-term prescription outweigh the benefits" (Remillard et al, 2019).

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

Cannabis

Chronic pain is currently and historically the most common qualifying condition reported by medical cannabis patients (64.9%) (Boehnke et al, 2019).

An examination of the evidence for medical cannabis in chronic pain found poor study design and no proof of efficacy (Campbell et al, 2019).

Transcranial magnetic stimulation (TMS)

TMS employs electromagnetic technology to deliver small electric currents to the cortex of the brain (see Chapter 29). It is used in the management of major depressive disorder and post-stroke rehabilitation.

TMS has been reported as effective in the treatment of chronic pain for a decade (Picarelli, 2010). In a recent review of 22 TMS studies, Baptista et al (2019) found Level A evidence for TMS over the motor cortex for fibromyalgia and neuropathic pain and Level B evidence for TMS for various other conditions, including complex regional pain syndrome and migraine. There is also some early evidence that TMS may be effective in the treatment of phantom pain and non-painful phantom sensations (Nardone et al, 2019).

References

Apkarian A, Sosa Y, Sonty S, Levy R, Harden R, Parrish T, Gitelman D. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. Journal of Neuroscience 2004; 24:10410-10415.

Australian Pain Society. Waiting in Pain. National Pain Summit, Canberra, Australia, March 11, 2010.

Balarajan R, Yuen P, Soni Raleigh V. Ethnic differences in general practitioner consultation. British Journal of Medicine 1989; 299:958-960.

Baliki M, Geha P, Apkarian A, Chialvo D. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. Journal of Neuroscience 2008; 28:1398-1403.

Baptista A, et al. Latin American and Caribbean consensus on…neuromodulation for chronic pain. Rain Rep. 2019; 4: e692.

Bernstein C, Albrecht K, Marcus D. Milnacipran for fibromyalgia: a useful addition. Expert Opin Pharmacother 2013, in press.

Bass C, Yates G. Why does psychiatry continue to ignor the problem of chronic pain? www.thelncet.com/psychiatry Vol 6, January 2019: 10-12.

Birke H, et al Tramadol use in Norway. Pharmacoepidemiol Drug Saf 2019; 28: 54-61.

Boehnke K, et al. Qualifying conditions of mental cannabis license holders in the US. Health Aff (Millwood) 2019; 38: 295-302.

Buckalew N, Haut M, Aizensten H, et al. White matter hyperintensity burden and disability in older aldults: is chronic pain a contributor? Physical Medicine and Rehabilitation 2013; in press.

Burgmer M, Gaubitz M, Konrad C, Wrenger M, Hilgart S, Heuft G, Pfleiderer B. Decreased gray matter volumes in the cingulo-frontal cortex and amygdale in patients with fibromyalgia. Psychosomatic Medicine 2009; 71:566-573.

Blyth F, March L, Brnabic A, Jorm L, Williamson M, Cousins M. Chronic pain in Australia: a prevalence study. Pain 2001; 89:127-134.

Breivk H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life and treatment. European Journal of Pain 2006; 10:287-333.

Campbell G, et al. Understanding the evidence for medical cannabis and cannabis-based medicines for the treatment of chronic non-cancer pain. Eur Arch Psychiatry Clin Neurosci 2019; 269: 135-144.

Ceko M, Bushnell M, Fitzcharles M, Schweinhardt P. Fibromyalgia interacts with age to change brain. Neuroimage Clin 2013; 3: 249-260.

Chung J, Zeng Y, Wong T. Drug therapy for the treatment of chronic nonspecific low back pain. Pain Physician 2013; 16: E685-704.

Crossin R, et al. Pregabalin misuse-related ambulance attendances in Victoria, 2012-2017: characteristics of patients and attendances. Med J Aust. 2019 Feb;210(2):75-79.

Fishbain D. Evidenced-based data on pain relief with antidepressants. Annals of Medicine 2000; 32:305-316.

Flor H, Braun C, Elbert T, Birbaumer. Extensive reorganization of primary somatosensory cortex in chronic back pain patients. Neuroscience Letters 1997; 224:5-8.

Grachev I, Fredrickson B, Apkarian A. Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. Pain 2000; 89:7-18.

Gwilym S, Keltner J, Warnaby C, Carr A, Chiz B, Cessell I, Tracey I. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. Arthritis and Rheumatism 2009; 61:1226-1234.
Jackson W, et al. Physical functioning and mindfulness skills training in chronic pain: a systematic review. J Pain Res 2019;12: 179-189.
Kanazi G, Johnson R, Dworkin R. Treatment of postherpetic neuralgia. Drugs 2000; 59:1113-1126.
Letzen J, et al. Altered mesocorticolimic functional connectivity in chronic low back pain patients at rest and following sad mood induction. Brain Imaging and Behavior 2019; Published online: 15 March 2019.
Macfarlane G, Hunt I, Silman A. Role of mechanical and psychosocial factors in the onset of forearm pain: prospective population base study. British Medical Journal 2000; 321:676-679.
McNaughton D, et al. Whether chronic pain is medically explained or not does not moderate the response to cognitive-behavior therapy. J Psychosom Res 2019; Mar 26 [Epub ahead of print]
Massaly N, et al. Pain-induced negative affect is mediated via recruitment of the nucleus accumbens kappa opioid system. Neuron2019; 102: [Epub ahead of press]
May A. Morphing voxels: the hype around structural imaging of headache patients. Brain 2009; 132:1419-1425.
Merskey H. Pain terms: a list with definitions and a note on usage. Recommended by the International Association fro the Study of Pain (IASP) Subcommittee on Taxonomy. Pain 1979; 6:249-252.
Merskey H, Bogduk N. Classification of Chronic Pain, 2nd Ed. IASP Press, Seattle, 1994.
Mifflin K, Kerr B. The transition from acute to chronic pain. Can J Anaesth 2013 Nov 26 [Epub ahead of print].
Nardone R, et al. Transcranial magnetic stimulation in subjets with phandom pain and non-painful phantom sensations. Brain Research Bulletin 2019; 148 [Epub ahead of print]
Nebel M, Gracely R. Neuroimaging of fibromyalgia. Rheuma Dis Clinics of North Amreica 2009; 35:313-327.
Obermann M, Rodriguez-Raecke R, Naegel S. et al. Gray matter volume reduction reflects chronic pain in trigeminal neuralgia. Neuroimage 2013, in press.
Picarelli H, et al. repetitive transcranial magnetic stimulation is efficacious… Journal of Pain 2010; 11: 1203-1210.
Pridmore S. Managing Chronic Pain: A Biopsychosocial Approach. Martin Dunitz: London, 2002.
Remillard D, et al. Oxycodone's unparalled addictive potential. Curr Pain Headache Rep 2019; 23(2): 15. Doi: 10.1007/s11916-019-0751-7.
Rhudy J, et al. Sensory, affective, and catastrophizing reactions to multiple stimulus modalities…J Pain Feb 22 [Epub ahead of print]
Rodriguez-Raecke R, et al. Brain gray matter decrease in chronic pain…J Neurosci 2009; 29: 13746-13750.
Schmidt-Wilcke T, Hierlmeier S, Leinisch E. Altered regional brain morphology in patients with chronic facial pain. Headache 2010, in press.

Seminowicz D, Labus J, Bueller J, Tillisch K, Naliboff B, Bushnell M, Mayer E, Regional gray matter density changes in brains of patients with irritable bowel syndrome. Gastroenterology 2010, in press.
Sindrup S, Jensen T. Pharmacologic treatment of pain in polyneuropathy. Neurology 2000; 55:915-920.
Silverman D, Munakata J, Ennes H, Mandelkern M, Hoh C, Mayer E. Pegional cerebral activity in normal and pathological perception of visceral pain. Gastroenterology 1997; 112:64-72.
Toth C. Substitution of gabapentin therapy with pregabalin therapy in neuropathic pain due to peripheral neuropathy. Pain Medicine 2010; 11:456-465.
Van Middelkoop M, Rubinstein S, Verhagen A, Ostelo R, Koes B, van Tulder M. Exercise therapy for chronic non-specific low-back pain. Best Pract Res Clin Rheumatol 2010; 24:193-204.
Walker J, Holloway I, Sofaer B. In the system: the lived experience of chronic back pain from the perspectives of those seeking help from pain clinics. Pain 1999; 80:621-628.