# Depression and chronic pain


## Summary

- Chronic pain and major depression commonly occur together.
- Major depression in patients with chronic pain is associated with decreased function, poorer treatment response and increased health care costs.
- The experience and expression of chronic pain vary between individuals, reflecting complex and changing interactions between physical, psychological and social processes.
- The diagnosis of major depression in patients with chronic pain requires differentiation between the symptoms of pain and symptoms of physical illness.
- Antidepressants and psychological therapies can be effective and should be delivered as part of a coordinated, cohesive, multidisciplinary pain management plan.


Chronic pain and depression are frequently comorbid.[1] The presence of depression in a patient with chronic pain is associated with decreased function,[1] poorer treatment response[2,3] and increased health care costs.[4] An accurate diagnosis of major depression can be challenging in the setting of comorbid chronic pain. Antidepressants and psychological treatments can be effective and are best delivered as part of a coordinated, cohesive, multidisciplinary pain management plan. Here, we describe the current approach to the assessment and management of major depression in patients with chronic pain.

## Biological basis of pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[5] Pain can be considered chronic when it persists for more than 1 month after anticipated tissue healing, or if it has been present for at least 3 of the previous 6 months.[6] A differentiation is made between neuropathic and nociceptive pain, reflecting different pathological mechanisms, clinical features and treatments. Neuropathic pain is caused by a lesion or disease involving the nervous system. It may have signs of an altered pain response (allodynia, hyperalgesia) and is treated with agents targeting the nervous system abnormality. Nociceptive pain occurs as a consequence of actual or threatened damage to non-neural tissue. It reflects a normally functioning somatosensory nervous system and responds to general analgesics and anti-inflammatory drugs.

Chronic pain is reported by 18.6% of Australian adults. It occurs more commonly in women and those who are poorly educated, unemployed, older, disabled or in compensation systems.[6] Common causes are joint arthritis, degenerative disc disease, traumatic injuries and various types of headache.[7] Chronic pain can also occur as part of a generalised pain syndrome, such as fibromyalgia.

The emergence of chronic pain has been associated with a range of physical, psychological and social risk factors. These factors interact in complex and dynamic ways, often conceptualised within a biopsychosocial framework.[8] Biological research has identified potential mechanisms for chronic pain in nociception, nerve conduction, regulation of spinal cord neurones, neuronal plasticity and gene expression.[9] For example, there is evidence that neuroplastic change arising from poorly treated persistent pain can lead to sensitisation, defined as an "increased responsiveness of neurons to their normal input or recruitment of a response to sub-threshold inputs".[10] Neuroplastic change is one possible explanation for the altered pain perception, persistence of pain beyond tissue healing, and resistance to commonly used analgesics that are frequently found in chronic pain.

## Pain and depression

The range of pain experiences is wide and varied. An individual's response to chronic pain reflects characteristics of the pain and the person's thoughts and behaviour developed during the course of the illness, which are subject to positive and negative reinforcement.[11] The daily challenges of chronic pain that are commonly described include decreased enjoyment of normal activities, loss of function, role change and relationship difficulties.[8] Uncertainty about ever being pain-free or the possibility of worsening pain are accompanied by feelings of anxiety, sadness, grief and anger. For some people, the burden of pain is difficult to manage and may lead to the emergence of a mental disorder.

Maladaptive responses to pain can, in themselves, worsen the pain experience and further impair function. The presence of catastrophisation, with excessive rumination about the pain, magnification of distress and excessive helplessness, is associated with a poorer response to pain treatments and greater disability.[12] For example, in patients with low back pain, a cycle of excessive fear of movement leading to deconditioning, further worsening pain and further fear — termed fear avoidance — has been found to be more predictive of disability than pain intensity.[13] Behaviour such as grimacing or groaning, reduced levels of activity, guarding against movement, and the use of protective devices is often linked with negative pain cognitions, and may also hinder recovery.

Major depression is the most common mental illness associated with chronic pain. High rates of generalised anxiety disorder, post-traumatic stress disorder and substance misuse have also been described.[14] The lifetime prevalence of major depression in Australia is 11.6%,[15] but it is 1.6 times higher in those reporting arthritis.[15] In Canada, the prevalence of depression is three times greater


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**MJA Open 2012; 1 Suppl 4: 17–20**
**doi: 10.5694/mjao12.10589**

in those with chronic back pain.[16] In patients with chronic pain presenting for treatment, the prevalence of major depression is 30%–40%.[17]

There are several ways pain and major depression may be associated, one or more of which may be present in a single patient. First, the psychological and physical distress of persistent pain interacting with individual and social vulnerability may precipitate an episode of major depression.[18] Common markers of vulnerability to major depression are a past personal or family history of depression, developmental deprivation, early loss of a parent, and substance misuse.[19] Second, depression may be a precursor to, and in some way contribute to, the pain. Pain tolerance is decreased in major depression, and somatic preoccupation can be a prominent symptom, especially in older people. Of note, more than half of the patients presenting with major depression in primary care report some pain.[19] In these circumstances, there can be a delay in making the diagnosis, especially when anhedonia predominates over lowered mood. Another proposed mechanism is that chronic pain is a subtype of depression.[20] Serotonergic and noradrenergic neurotransmitters have been implicated in both conditions, and they share a clinical pattern of persistence beyond the precipitant. However, there is little other evidence to support this notion. The final way in which chronic pain and major depression may be associated is when both arise out of a common underlying process. This may be a neurological illness, such as multiple sclerosis, or one where the mechanism is not well understood, like fibromyalgia.

## Assessment

An assessment of major depression in a patient with chronic pain should be done in conjunction with a pain assessment. A pain assessment characterises the pain, identifies prominent cognitions and behaviour, differentiates nociceptive and neuropathic pain, and determines the impact of pain on function. A comprehensive assessment may include input from a range of disciplines, including pain medicine.

The diagnosis of depression in patients with chronic pain is made more complex by an overlap between depressive symptoms and those relating to the comorbid physical illness and pain (see also Olver and Hopwood, *page 9*).[21,22] According to the *Diagnostic and statistical manual of mental disorders, 4th edition, text revision* (DSM-IV-TR), a diagnosis of major depression requires depressed mood or diminished interest or pleasure over 2 weeks, with additional somatic symptoms (sleep disturbance, fatigue, diminished ability to think, weight disturbance) and cognitive symptoms (worthlessness, guilt, suicidality), all leading to significant distress or dysfunction.[23] However, most patients with chronic pain describe decreased initiative,[18] anhedonia,[18] and sleep and appetite disturbance. Several approaches may be used to overcome this diagnostic overshadowing, each representing a different balance of sensitivity and specificity.[24]

First, the inclusive method allows for all symptoms to be included in making the diagnosis, even if they could be explained by physical illness or pain. This approach has the advantage of simplicity and reliability, but can result in overdiagnosis of major depression.

Second, the exclusive method requires that somatic symptoms are not used, leaving the cognitive symptoms from which to make the diagnosis. Patients with chronic pain and depression are more likely to describe increased sadness, reduced self-worth, lack of meaning and suicidality than those with pain alone,[18] giving support to an exclusive approach. The exclusive method deals well with diagnostic overshadowing but at the cost that some cases, including in patients with more severe forms of depression manifest in somatic complaints, might be missed.

Third, using the substitutive method, somatic symptoms of depression are replaced with additional cognitive or affective symptoms. These may include hopelessness, pessimism, irritability, tearfulness, feeling punished, or social withdrawal. There is no consensus on which symptoms can be used as substitutes, nor the total number required.

Finally, the aetiological approach requires judgement by the clinician as to whether the symptoms are related to the physical illness or the depression. This method is supported by the DSM-IV-TR,[23] but has the disadvantage of the reduced reliability implicit in making this judgement.

No one approach has a clear advantage over the others. In some cases, the same conclusion will be reached regardless of the method, as in a patient with clear mood change, rumination, pessimism, hopelessness, guilt, low self-worth, and a depressed affect on mental state examination. When the diagnosis is less clear, as in a patient with a fluctuating affect, less prominent cognitive symptoms or marked somatic symptoms, interviewing collateral historians, such as the patient's family, to determine a clear and persistent change in mental state over time can be useful.

## Management

The management of major depression in patients with chronic pain should occur as part of a coordinated approach to pain management, with attention to relevant psychological processes and social issues. In addition to specific interventions, pain management involves identifying and establishing shared treatment goals, collaborative multidisciplinary care and a mutual understanding of the different practitioner roles and responsibilities.

### Pharmacological treatment

Research into the pharmacological treatment of major depression in patients with chronic pain has predominantly focused on tricyclic antidepressants (TCAs). TCAs have analgesic properties independent of their antidepressant effect.[25] The presumed mode of analgesic action is through enhancing descending spinal noradrenergic and serotonergic inhibitory neurones.[26] The doses used in analgesic studies[27] and in pain medicine (10–50 mg) are lower than those used for depression (100–200 mg).[28] Analgesic studies have demonstrated decreased depressive symptoms alongside reductions in pain, but the treatment of major depression has not been established at

these doses. If TCAs are used to treat major depression, antidepressant doses are required.[28] Higher doses lead to increased side effects, including sedation, blurred vision, orthostatic hypotension, falls and an increased risk of delirium. Concern about cardiac toxicity, especially in overdose, has led to caution around the use of TCAs as antidepressants. In patients without cardiovascular disease and in whom concerns about self-harm are low, TCAs still have a role, especially when other antidepressants have not been effective. The secondary amines nortriptyline and desipramine are better tolerated than imipramine and amitriptyline in medically ill patients[29] and may also be preferable in patients with pain.

A smaller body of research exists in relation to the newer antidepressants and their analgesic properties. Of particular interest are the serotonin–noradrenaline reuptake inhibitors (SNRIs), given their similarities to TCAs. Duloxetine, an SNRI with balanced inhibition of serotonin and noradrenaline reuptake, is effective for both neuropathic[30] and nociceptive pain[31] — an effect independent of reductions in depression or anxiety. The United States Food and Drug Administration has approved duloxetine for the treatment of fibromyalgia and painful diabetic neuropathy at a dose of 60 mg daily.[32] Common side effects of duloxetine are nausea, vomiting, constipation, dry mouth and insomnia, but these are often mild and transient. The evidence for venlafaxine, in which serotonin reuptake inhibition predominates, especially at low doses, is less robust. Case reports[33] and some study evidence[34] suggest potential for analgesic activity in neuropathic pain at doses of around 75 mg.

The management of comorbid major depression and chronic pain with antidepressants requires clarity around the aims of treatment. TCAs and venlafaxine at analgesic doses are subtherapeutic for major depression. Combining TCAs with selective serotonin reuptake inhibitors (SSRIs) has the potential to induce a serotonergic syndrome. Although there is evidence for response of major depression to duloxetine at doses of 60 mg, some patients require doses of 120 mg.[35] To treat major depression effectively, antidepressants need to be used at therapeutic doses for at least 4 weeks, before increasing to higher doses or changing to another agent. SSRIs, which have limited analgesic effect, are often used as first-line treatment of major depression. Among these, escitalopram and sertraline are most efficacious and best tolerated,[36] with escitalopram having a low propensity for drug interaction through induction of liver enzymes. Even with optimal treatment, however, antidepressants may not be effective in inducing remission of major depression, especially in the context of severe and prolonged pain.[37]

### Psychological interventions

Psychological therapies are used to treat major depression and reduce depressive symptoms in patents with chronic pain. The most robust evidence for their use in the treatment of major depression is derived from randomised controlled trials involving the general population and patients with other medical comorbidities. In a landmark study, 12 sessions of standardised and adherent cognitive behaviour therapy (CBT) or interpersonal therapy were found to be equivalent to imipramine (200 mg) and more effective than placebo or supportive therapy in treating major depression.[38] A study of CBT and antidepressant therapy in patients with multiple sclerosis showed lower rates of major depression in the two treatment groups, compared with the group receiving treatment as usual.[39] The negative cognitions challenged in CBT for major depression relate to the world (pessimism), the future (hopelessness) and the self (low self-worth), and the focus of behaviour change is withdrawal and cessation of pleasurable activities. The aim of CBT for major depression is remission and recovery.

Psychological therapies are effective in reducing depressive symptoms in patients with a medical illness[40] or chronic pain.[41] CBT in patients with chronic pain challenges maladaptive pain cognitions and behaviour, such as catastrophisation and fear avoidance. The aim of CBT in regard to chronic pain is symptom reduction and functional improvement, rather than complete pain relief. Within a multidisciplinary pain program, these methods can increase perceived control and decrease catastrophising, leading to a decrease in pain and depressive symptoms and improved function.[42] Techniques that address change, loss, relationship difficulties, acceptance and self-regulation may also be useful.[43] Pharmacological and psychological treatments are commonly combined, an approach that has been shown to be effective in the management of depressive symptoms in patients with musculoskeletal pain in primary care.[44]

## Conclusions

Major depression is common in patients with chronic pain. Making the diagnosis can be difficult and is best done as part of a wider pain assessment. Depression is treated pharmacologically and psychologically, although treatment efficacy can be reduced in patients with severe and prolonged pain. Collaboration with other treating clinicians and specialist advice are often useful, especially in complex cases. Despite these challenges, successful treatment of major depression will reduce pain and improve function and quality of life for patients with chronic pain.

**Competing interests:** No relevant disclosures.

**Provenance:** Commissioned by supplement editors; externally peer reviewed.

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