When depression hurts

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Introduction

Depression is a disorder of the body as much as of the mind. The traditional understanding of pain and depression as separate conditions with overlapping symptoms has evolved through research into an understanding that pain and depression share pathophysiological mechanisms. These shared pathophysiological mechanisms include origins, mechanisms and neurotransmitters, resulting in shared treatments. In addition, pain and depression have a reciprocal relationship in that each heightens the severity of the other. Failure to eliminate the pain symptoms reduces the chances of full recovery from depression: it keeps depressed people from regaining full function in their personal and professional lives, and it raises the danger of suicide. Furthermore, the presence of a depressed mood increases the perception of the severity of, and contributes to distress associated with pain.

What is pain?

The International Association for the Study of Pain (IASP), defines pain as an emotional experience associated with actual or potential tissue damage. Pain is a multidimensional experience that includes discriminative, affective, motivational and cognitive components mediated by spinal, brainstem and cerebral functioning, modulated through forebrain mechanisms. Pain, as a sub-modality of somatic sensation, has been defined as a “complex constellation of unpleasant sensory, emotional and cognitive experiences provoked by real or perceived tissue damage and manifested by certain autonomic, psychological, and behavioural reactions”.

The severity of pain does not only bear a simple relationship to the degree of tissue damage. In addition to various genetic, epigenetic, and environmental factors, interpersonal variability in the engagement of emotional cortico-limbic circuitry by pain may explain why some patients develop chronic pain conditions, and others do not. This is supported by consistent findings of chronic painful symptoms in stress-related mood and anxiety disorders, with up to 80% of patients with depression reporting comorbid pain conditions, while the presence of continuous pain increases the severity and frequency of depressive symptoms with up to four times. The comorbidity of chronic pain and chronic depression makes it difficult to pinpoint the temporal and causal relationship, but the correlation between the two conditions is clear. People in pain who are also depressed become heavy consumers of medical services, even if they have no severe underlying illness. Pain slows recovery from depression, and depression makes pain more difficult to treat (e.g. due to lack of motivation for compliance). Both pain and depression exacerbate themselves by changing both brain function and behaviour. Depression leads to isolation, and isolation leads to further depression; pain causes fear of movement, and immobility creates the conditions for further pain. When depression is treated, the emotional impact of pain diminishes, while when pain is alleviated, so is much of the suffering that causes depression.

The biological pathways of pain

Pain processing typically involves transmission and modulation of nociceptive signals along a predictable pathway (Figure 1). Cutaneous nociceptors are an extremely heterogeneous group of neurons. These nociceptors are generally electrically silent and transmit all-or-none action potentials only when stimulated by external noxious stimuli (temperature extremes, intense pressure, or chemicals). However, nociceptor activity alone does not lead to the perception of pain. Peripheral information needs to reach higher cortical centres and depends on the frequency of action potentials in primary afferents, temporal summation of pre- and postsynaptic signals, and central influences. Acute pain is divided into fast pain (which is sharp, easily localisable and does not cause much emotional anguish) and slow pain (which is burning, aching, throbbing and triggers autonomic and emotional reactions). Fast pain is mediated by small lightly myelinated Aδ (A-delta class)-fibres, while slow pain is mediated by unmyelinated C-fibres which are stimulated by nociceptive chemicals (serotonin, substance P, prostaglandins) released after the damage.

Pain modulation occurs at both spinal cord level and centrally. Peripheral nociceptive neurons synapse in the dorsal root ganglia where interneurons cause inhibitory/excitatory modulation. Fast and slow synaptic transmission are enhanced in large part by glutamate and peptides (e.g. substance P, CGRP). Of particular importance to pain perception is the plasticity in synaptic strength (i.e. the ability to enhance homosynaptic connections) by both primary afferents and the relay and interneurons they drive, presynaptic and postsynaptic modulation by descending facilitatory pathways.
and inhibitory pathways in the spinal cord, and the efferent aspects of nociceptor function activated by strong GABAergic/glycinergic depolarisation of presynaptic terminals leading to the dorsal root reflex. Secondary spinal projection neurons then transmit the information to two areas of the brainstem – the rostral ventral medulla and periaqueductal gray matter – where they are further modulated and relayed to the thalamus. All afferent neurons end in the thalamus where they synapse with three sets of neurons: those projecting to the somatosensory cortex ("where is the pain?") and the frontal cortex ("what am I going to do about the pain?").

There is a significant overlap between pathways involved in mood and pain regulation – especially the serotonergic (5-HT)/norepinephrine (NE) pathways which are central to the gated control theory. Both 5-HT and NE have ascending pathways which are central to the gated pathways involved in mood and pain regulation – especially the serotonergic (5-HT)/norepinephrine (NE) pathways which are central to the gated control theory. Secondary spinal projection neurons then transmit the information to two areas of the brainstem – the rostral ventral medulla and periaqueductal gray matter – where they are further modulated and relayed to the thalamus. All afferent neurons end in the thalamus where they synapse with three sets of neurons: those projecting to the somatosensory cortex ("where is the pain?") and the frontal cortex ("what am I going to do about the pain?").

Converging lines of evidence now also suggest that the pathophysiology of pain is mediated to a substantial degree via allostatic neuroadaptations in reward- and stress-related brain circuits.

Acute pain activates dopamine (DA) transmission in the brain’s reward and motivational centres, whereas prolonged periods of pain produce the opposite effect (within system adaptation) clinically manifested by anhedonia and diminished motivational/incentive salience of natural reinforcers, i.e. the reward deficiency state (RD). Allostatic adjustment (processes that attempt to normalise the stress on the system) to excessive dopaminergic transmission in response to recurrent pain leads to a between-system adaptation involving the central and basolateral amygdala nuclei, the bed nucleus of the stria terminalis, the lateral tegmental noradrenergic nuclei of the brain stem, and the hippocampus. This leads to massive surges of corticotropin-releasing factor (CRF), NE, glutamate and dynorphin – leading to the anti-reward state (AR).

Recurrent pain or ongoing pain may contribute to surges of these stress-related chemicals – presenting not only with ongoing pain, but also with symptoms of depression which include poor motivation, apathy, and anhedonia. Glutamatergic sensitisation promotes overlearning of the motivational salience of pain, analgesia and cues that predict the onset or severity of pain so that pain is constantly perceived to be worse than expected (i.e. “catastrophising”). These effects result in an unstable positive feedback loop wherein the combined reward RD and AR model (CReAM) drives further enhancement of pain and thus contributes to progressive worsening of the clinical condition and an end-stage outcome of chronic, intractable pain (Figure 2).

In chronic pain states, inflammatory factors and sensitised receptors in the skin are thought to cause an abnormal increase in the transmission of nociceptive signals from the periphery as well as either a lack of inhibition or increased excitation, or both, at the spinal cord, brainstem or cortical levels, called “central sensitisation”. In addition, according to the CReAM model, biopsychosocial variables modulating brain reward, motivation and stress functions can interact in a “downward spiral” fashion to exacerbate the intensity, chronicity and comorbidities of chronic pain syndromes – amplifying the aversive physical and emotional aspects of pain. Such processes may further contribute to treatment resistance (to current pharmacotherapies) in chronic pain.

Neuroimaging has become an increasingly important and popular means of studying how the brain perceives and processes chronic pain. Various neuroimaging modalities, such as positron emission tomography, encephalography, magnetoencephalography, single-photon-emission computed tomography, magnetic resonance imaging (MRI), and functional MRI, have contributed to elucidating many of the neural correlates regarding factors well known to modulate the experience of pain, including attention, anticipation, empathy, placebo, meditation, fear/anxiety and reward.

Evidence from functional MRI of the brain confirmed that depressive symptoms are related to the cerebral processing of pain and indicated an overlap in the areas for pain processing and sensation, and major depressive-related alterations in the brain. Pain processing has been associated with involvement of...
primary and secondary somatosensory cortex, thalamus, insular cortex, amygdala, anterior cingulate cortex, and the prefrontal cortex. Major depressive disorder (MDD) often exhibited lateral and medial frontal hypo- and hyper-metabolism, and metabolic changes in limbic regions such as insula and amygdala. This activation of the prefrontal cortices might reflect an underlying prefrontal psychopathology in depression. Negative affective states therefore clearly influence pain processing in terms of augmented pain experience. It is therefore crucial that both mood and pain should be treated simultaneously.

The optimal management of patients suffering from these two hurtful conditions

Patients with chronic pain can be challenging to manage and historically providers have relied on opiates to treat pain. However, recent studies have brought into question the safety and efficacity of chronic opiate therapy in the non-cancer population. Nonsteroidal anti-inflammatory drugs (NSAIDs) affect varying degrees of pain modulation through the inhibition of prostaglandin (PG) synthesis. NSAIDs have been shown to be effective in the treatment of chronic lower back pain, as well as chronic osteoarthritis. A recent meta-analysis has also demonstrated the opioid-sparing effect (20–30%) of the addition of an NSAID to a pain management regimen.

Almost every drug used in psychiatry can also serve as a pain medication. Relieving anxiety, fatigue, depression, or insomnia with mood stabilisers, benzodiazepines, or anticonvulsants will also ease any related pain. The most versatile of all psychiatric drugs, the antidepressants, have an analgesic effect that may be at least partly independent of their effect on depression since it seems to occur at a lower dose. Other strategies include the use of anticonvulsants (e.g. carbamazepine, gabapentin, and pregabalin), topical agents (e.g. lidocaine and capsaicin), cannabinoids, botulinum toxin, and non-pharmacological strategies such as physical therapy, progressive muscle relaxation, hypnosis, meditation, and cognitive and behavioural therapies (CBT). CBT teaches patients how to avoid fearful anticipation, banish discouraging thoughts, and adjust everyday routines to ward off physical and emotional suffering due to chronic pain. See Table I.

Summary

Hurting bodies and suffering minds often require the same treatment.

Depression has long been associated with pain. Although it was once thought that people with pain were somehow “denying” their emotional disorder and converting it into bodily pain, evidence now suggests that somatic complaints are the way some people become depressed. For a substantial number of people, possibly up to half of depression sufferers, bodily pain is the way depression presents itself. Failure to eliminate pain
<table>
<thead>
<tr>
<th>Medication class</th>
<th>Medication</th>
<th>Starting dosage</th>
<th>Titration</th>
<th>Maximum dosage</th>
<th>Duration of adequate trial</th>
<th>Major side-effects</th>
<th>Precautions</th>
<th>Other benefits</th>
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<tr>
<td><strong>Antidepressant medications</strong></td>
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<td>Secondary amine TCAs</td>
<td>Nortriptyline</td>
<td>25 mg at bedtime</td>
<td>Increase by 25 mg daily every 3–7 d, as tolerated, until pain relief</td>
<td>150 mg daily; if blood level of active drug and its metabolite is &lt; 100 ng/mL (mg/mL), continue titration with caution</td>
<td>6–8 wk with ≥ 2 wk at maximum tolerated dosage</td>
<td>Sedation, dry mouth, blurred vision, weight gain, urinary retention</td>
<td>Cardiac disease, glaucoma, suicide risk, seizure disorder, concomitant use of tramadol</td>
<td>Improvement of depression, improvement of insomnia, low cost</td>
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<td></td>
<td>Desipramine</td>
<td>125 mg at bedtime</td>
<td>Increase by 25 mg daily every 3–7 d, as tolerated, until pain relief</td>
<td>150 mg daily; if blood level of active drug and its metabolite is &lt; 100 ng/mL (mg/mL), continue titration with caution</td>
<td>6–8 wk with ≥ 2 wk at maximum tolerated dosage</td>
<td>Sedation, dry mouth, blurred vision, weight gain, urinary retention</td>
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<td></td>
<td>Venlafaxine</td>
<td>75 mg once daily</td>
<td>Increase by 75 mg each week, as tolerated until pain relief</td>
<td>225 mg daily</td>
<td>4–6 wk</td>
<td>Nausea</td>
<td>Concomitant use of tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation</td>
<td>Improvement of depression</td>
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<td>SSNRIs</td>
<td>Duloxetine</td>
<td>30 mg once daily</td>
<td>Increase to 60 mg once daily after 1 wk</td>
<td>60 mg twice daily</td>
<td>4 wk</td>
<td>Nausea</td>
<td>Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol</td>
<td>Improvement of depression</td>
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<td>Venlafaxine</td>
<td>75 mg once daily</td>
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<td>Calcium channel α₂-δ ligands</td>
<td>Gabapentin</td>
<td>100–300 mg at bedtime or 100–300 mg 3 times daily</td>
<td>Increase by 100–300 mg 3 times daily every 1–7 d, as tolerated, until pain relief</td>
<td>3 600 mg daily (1 200 mg 3 times daily); reduce if impaired renal function</td>
<td>3–8 wk for titration + 2 wk at maximum dose</td>
<td>Sedation, dizziness, peripheral oedema</td>
<td>Renal insufficiency</td>
<td>Improvement of sleep disturbance, no clinically significant drug interactions</td>
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<td>Pregabalin</td>
<td>50 mg 3 times daily or 75 mg twice daily</td>
<td>Increase to 300 mg daily after 3–7 d, then by 150 mg/d every 3–7 d, as tolerated, until pain relief</td>
<td>600 mg daily (200 mg 3 times daily or 300 mg twice daily); reduce if impaired renal function</td>
<td>4 wk</td>
<td>Sedation, dizziness, peripheral oedema</td>
<td>Renal insufficiency</td>
<td>Improvement of sleep disturbance, improvement of anxiety, no clinically significant drug interactions</td>
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<td>Topical lidocaine</td>
<td>5% lidocaine patch</td>
<td>Maximum of 3 patches daily for a maximum of 12 h</td>
<td>None needed</td>
<td>Maximum of 3 patches daily for a maximum of 12–18 h</td>
<td>3 wk</td>
<td>Local erythema, rash</td>
<td>None</td>
<td>No systemic side-effects</td>
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<td>Opioid agonists</td>
<td>Morphine, oxycodone, methadone, levorphanol</td>
<td>10–15 mg morphine every 4 h or as needed (equianalgesic dosages should be used for other opioid analgesics)</td>
<td>After 1–2 wk, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed</td>
<td>No maximum dosage with careful titration; consider evaluation by pain specialist at relatively high dosages (e.g. 120–180 mg morphine daily; equianalgesic dosages should be used for other opioid analgesics)</td>
<td>4–6 wk</td>
<td>Nausea/vomiting, constipation, drowsiness, dizziness</td>
<td>History of substance abuse, suicide risk, driving impairment during treatment initiation</td>
<td>Rapid onset of analgesic benefit</td>
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<td>Tramadol</td>
<td>50 mg once or twice daily</td>
<td>Increase by 50–100 mg daily in divided doses every 3–7 d, as tolerated, until pain relief</td>
<td>400 mg daily (100 mg 4 times daily); in patients aged &gt; 75 y, 300 mg daily</td>
<td>4 wk</td>
<td>Nausea/vomiting, constipation, drowsiness, dizziness, seizures</td>
<td>History of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant use of SSRI, SNRI, or TCA</td>
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symptoms reduces the chances of full recovery. Persistent pain typically keeps depressed people from regaining full function in their personal and professional lives, and it raises the danger of suicide. The goal of treatment is not just comfort or the absence of symptoms but restoring the capacity to lead a productive life.

References: