Editorial

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Depression and pain: is there a common pathway?

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Chronic pain, arbitrarily defined as that lasting longer than six months, is a clinical, social, and economic problem. It is often accompanied by feelings of low mood and despondency.

Whether chronic pain induces clinical depression or depression initiates psychosomatic pain (through physiological mechanisms) is difficult to prove. The burden of illness increases when patients suffer from both. Financial hardship and medical costs affect the quality of life which leads to difficulties in coping and further decreased functioning, making the treatment of both conditions more complicated. Therefore, better recognition, assessment, and treatment of comorbid pain and depression should, at least in theory, lead to better outcomes.

Pain is broadly categorized into three groups: nociceptive (any painful stimulus), neuropathic (for example, diabetes), and psychogenic. Nociceptive pain occurs with direct noxious stimuli. Neuropathic pain is a result of disease or injury to the nervous system or spinal cord. Psychogenic pain has no discernible physical origin. Although the precise physiological mechanisms are not entirely understood, there are two basic categories of sensory neurones. The first type is myelinated and fast conducting; the second is unmyelinated and slow conducting.

Acute pain which follows damage to tissue (an ankle sprain, for example) is usually correlated with hyperalgesia (an increase in the pain elicited by a noxious stimulus and felt as a sharp, burning sensation) and allodynia ('other' pain evoked by a normally innocuous stimulus) and serves to protect the injury from further trauma while allowing the damage to be repaired.

Depression is often a chronic disorder and though its symptoms may be alleviated by appropriate medication and other therapies, physical complaints tend to be more intractable. For example, fibromyalgia (FM), a syndrome characterized by widespread muscle pain and generalized tender points, is often associated with major depressive disorder.[1] However, although the vast majority of patients with fibromyalgia do not meet criteria for a psychiatric disorder, psychological symptoms are common. In a randomized controlled trial of primary care patients with musculoskeletal problems and depression, antidepressant medication followed by a self-management pain programme led to improvement in both.[2]The tricyclic antidepressant amitriptyline was traditionally used usually in small doses, to treat pain, with moderate success. In addition to its own intrinsic analgesic effect amitriptyline appears to enhance the effects of opioid analgesia. Other antidepressants are now in vogue; for example, duloxetine, a serotonin (5-HT)/noradrenaline (NA) reuptake inhibitor, is sometimes used for diabetic neuropathic pain.

Of the numerous neurotransmitters at least two, namely 5-HT and NA, may prove to be one common link between depression and pain. Both serotoninergic and noradrenergic pathways ascend from subcortical areas (brainstem, hypothalamus and thalamus) to the whole neocortex and mediate emotional and physiological responses.[3] Their pathways descend the spinal cord and suppress nociceptive inputs. Serotoninergic cell bodies located in the raphe nucleus in the brainstem, and noradrenergic neurones located in the locus coeruleus (also in the brainstem) send projections to various parts of the brain involved in the control of mood, appetite, sexual activity, attention and concentration. Theoretically at least, a dysfunction at the level of the serotoninergic and noradrenergic neurons could affect both ascending and descending pathways resulting in the psychological and physically painful symptoms of depression. Neurotransmitters may open or close the 'gate' on perception of painful stimuli. Therefore adrenergic and serotoninergic pathways from the brainstem to the spinal cord will inhibit incoming painful stimuli. This is perhaps an oversimplification as some sensory fibres enter via the ventral spinal roots.

The hypothalamic pituitary axis (HPA) is probably also involved. The hypothalamus, which synthesises and secretes neurohormones, has a wide range of physiological functions including regulation of thirst and hunger, sexual behaviour, defence reactions such as fear and rage, and circadian rhythm: disturbances of all these functions are frequently seen in depressed or anxious patients. The HPA is also affected in patients with physical stress as well as major depression, as shown by increased levels of adrenocorticotropic hormone and

cortisol in the plasma. Stimulation of the lateral areas of the hypothalamus produces a diffuse sympathetic discharge possibly because some areas of the hypothalamus control adrenaline and NA secretion. Prolonged stress associated with pain leads to depletion of central 5-HT and malfunction of other associated receptors.[4]

The hypothalamus and limbic system (whose boundaries are difficult to define) with its associated structures – the amygdala, hippocampus and septal nuclei, are involved in the mental and affective aspects of emotions. The amygdala, a cluster of nuclei in the medial temporal lobe, may have a role in the reciprocal relationship between pain and depression. The amygdala controls not only emotional behaviour but also memory. However, mixed results have been reported regarding the level of activity of the amygdala in response to pain.

Nociceptor afferents terminate within distinct regions of the dorsal horn and within the spinal cord, synapses are sites of considerable modification, hence the term 'gate' for the dorsal horn cells. The neurotransmitter for slow pain is believed to be substance P, and glutamate is the putative transmitter secreted by primary afferent fibres subserving fast pain.[5]

5-HT and NA neurotransmitter systems influence neuroplasticity in the brain. Most currently available antidepressants act through reuptake inhibition of either or both. Therefore, it would seem feasible to prescribe dual-action antidepressants when pain symptoms are associated with depression. However depressed patients with pain comorbidity are less likely to take antidepressant medications compared to those with depression alone. Also, individuals who develop pain or depression are at risk for developing the other, thus escalating the clinical management. Furthermore, when pain is refractory to treatment, it is associated with more depressive symptoms and worse depression outcomes, and vice versa. Depressive symptoms are very common in physically ill patients. Unfortunately, depression is often overlooked in pain patients because pain symptoms take priority or worse still, comorbid depression is not considered.

It is difficult to state with certainty whether or not unexplained pain is 'psychological'. Such an assumption might be perceived as demeaning and patronizing to patients and the suggestion of providing cognitive therapy misinterpreted as him/her overplaying their reaction to pain or that the pain is 'psychological'. Others do not like being labelled 'psychiatric', and are therefore reluctant to take antidepressants even when a physiological explanation is given. Pain perception involves physical and emotional factors and its primary function is to protect the organism from harm. It follows therefore, that pain thresholds and pain tolerance vary from individual to individual, and especially among patients with depression.

Antidepressants are frequently used in the treatment of depression and generalized anxiety disorders. Their use extends beyond these areas, however, and it is now accepted that antidepressants are efficacious in treating chronic pain syndromes in addition to their effects on psychological features such as low mood, inordinate guilt, or feelings of worthlessness. Because physical symptoms are often the main complaint in many depressed patients and pain is common as a presenting symptom, clinicians need to know about the dual use of antidepressants for both. Future antidepressants may involve neurotransmitters, other than 5-HT and NA, which could include dopaminergic pathways, opioid (antagonists of morphine-type drugs) receptors and the pentapeptides (enkephalins) which bind to these receptors.

Competing Interests
None declared
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