

# A patient with a chronic pain



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This essay will discuss the mechanisms of chronic pain and how it relates to the patient. The focus of this essay will be on the pathophysiology of chronic pain. Chronic pain management, psychological, sociological and public health issues will also be discussed.

## Section A

Mrs HR a 50 year old female who works as European Sales Manager for a large IT company presented to Royal South Hants Hospital Pain Clinic with worsening neck pain. HR has a constant severe and intense ache in right side of her neck with spasms in her right trapezius muscle. The pain is neither exacerbated nor relieved when pressure is applied. She has general background pain, aching and fatigue.

HR's pain is made worse by sitting or standing in an upright position for a prolonged period of time (> 2hours), vibrations from driving, prolonged movement/exercise and stress at work. Her pain can vary considerably throughout the day and often keeps her awake at night. Her pain is improved by lying flat and medication.

An MRI scan excluded any significant pathology or cord compression. She has general wear and tear of her neck muscles. Mrs HR has been seen by an orthopaedic surgeon, a pain clinic consultant, her GP, and a physiotherapist. Subjectively on a pain scale, the worst pain during an acute episode is 10/10, and the least pain experienced day to day is 3/10. On average the pain she experiences is 7/10.

In 1995 HR injured her neck in a swimming pool, when someone jumping in landed on top of her. In 1997 HR suffered whiplash following a road traffic accident. At the time of the incidents HR experienced minimal discomfort. However, in 2005 the pain started to become a burden to her. Since 2005 the pain has gradually increased in intensity and frequency and she has general achiness/stiffness.

In the past she has suffered from fibroids and migraines. She is allergic to tramadol which causes vomiting, excessive sweating and an increased heart rate. She has no significant family history and her systems review was unremarkable. On examination her reflexes, sensitivity, power and tone and coordination were unremarkable. HR is diagnosed as having nociceptive/inflammatory chronic pain due to previous damage to her deep neck muscles. The patient may also have some neuropathic pain but this has not been confirmed. She has completed pain questionnaires, including the McGill questionnaire.

Previous to her pain clinic appointment her medications included; gabapentin 300mg tds po, co-codamol 30/500 qds po and robaxin 750mg prn (during an acute episode, approximately twice a month). These were changed to; gabapentin 300mg qds po, dihydrocodeine 60mg bd modified-release po and nortriptyline 25mg nocte po. HR experiences constipation as a side effect of co-codamol. HR uses a TENS machine at home, she has a hydrotherapy pool and spa at home that helps her relax.

Mrs HR has lived with her husband, a barrister for 33 years. Her husband is understanding about her condition and would like her to give up her stressful

job. However, HR enjoys her job, claiming that it makes her happy. They have no known financial constraints and are not taking or have previously taken any legal action in relation to Mrs HR pain. HR is a non-smoker and does not drink alcohol. Chronic pain severely affects Mrs HR's day to day living; it reduces her general activity, mood and walking ability. She is unable to work normal hours as she is unable to concentrate when her pain is at its worst; as a result she has given up her social life to focus on her work. Her relationships with other people have suffered as a result of her chronic pain, so has her sleep and enjoyment of life.

## **Section B**

Chronic pain is an abnormal somatosensory processing in the peripheral and central nervous system that persists longer than would normally be expected relative to the stimulus. 1 The pain does not subside despite apparent healing of the initial injury and there is no known physiological purpose. Pain is a complex phenomenon that combines neurophysiological process with genetics, emotional state, attitudes, personality, circumstances and social context. 2, 3 A major risk factor for the development of chronic neck pain is a previous episode of neck/black pain and/or persistent pain elsewhere in the body. 4

HR has nociceptive/inflammatory somatic musculoskeletal chronic pain that is likely to be a result of her previous neck injuries. This section of the essay will focus on mechanisms of chronic pain development. It will outline peripheral and central pathophysiological changes that may have occurred in HR. Unfortunately however, it is not possible within the scope of this essay to detail the pathophysiological changes that can take place in the brain and

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the neuromatrix theory of pain. 5 This essay will not discuss neuropathic pain.

The disease process in chronic pain involves changes in the structure and function of the nervous system, as it is shaped and reshaped by the activity within. The nervous system has great plasticity. The CNS inhibits or amplifies the signals that the brain ultimately interprets as pain. 6 HR's chronic pain experiences include spontaneous pain, primary hyperalgesia (increased pain at the site of injury), secondary hyperalgesia (increased pain near the site of injury), and allodynia (pain caused by an innocuous stimuli).

Activation, modulation and modification are different forms of plasticity that can result in pain hypersensitivity. 6 Activation-dependant plasticity is where activation of nociceptive pathways manifests as a progressive increase in response of the system, to repeated stimuli. This can occur in nociceptive terminals in the periphery (autosensitisation) and in dorsal horn neurons (windup). Both these processes occur in normal physiological pain and usually resolve after tissue repair, as they are normally activity dependant and reversible. Autosensitisation and windup can be contributing factors in the development of peripheral and central sensitisation. 6, 7

Autosensitisation occurs when high threshold peripheral nociceptors become sensitive to lower threshold stimuli, this is due to changes in the transducers. The change in threshold of nociceptive neurons can also be due to an increase in the excitability of the peripheral nociceptive membrane terminal, this is termed heterosensitisation. 6

Windup occurs when repetitive low-frequency activation of nociceptors (C-fibres) in the periphery by noxious stimulus cause fast EPSP (excitatory post-synaptic potential) in the dorsal horn. <sup>8</sup> This results in co-release of neuromodulators and glutamate that produce slow EPSPs from wide dynamic range neurons. This results in temporal summation of nociceptive inputs and increased responsiveness of the neurons. Increased responsiveness also occurs when NMDA receptor currents, caused by peripheral inflammation removes the  $Mg^{2+}$  block at NMDA receptors. This increased receptor activation further stimulates  $Ca^{2+}$  channels and causes an increase in  $Ca^{2+}$  influx and intracellular  $Ca^{2+}$  release. This results in an increased action potential discharge from the neuron, which is known as windup. <sup>6, 9</sup>

Modulation of peripheral terminals is due to sensitising agents acting on receptors causing an inflammatory response. Central sensitisation is triggered by repetitive input from peripheral nociceptors which causes an increase in excitability of dorsal horn neurons. This causes an enhanced intensity of pain that outlasts the initial input. This process may require a low-level of pathology or inflammation in the periphery. Modulation can be due to numerous mechanisms and is potentially reversible. Mechanisms of modulation include phosphorylation of ion channels, receptors or regulatory peptides. This can change the intrinsic functional properties of expressed channels in the cell surface of primary sensory and dorsal horn neurons. Innocuous stimuli can cause an amplified response in the pain pathways in central sensitisation. This is linked to NMDA receptor activity and can involve AMPA receptors. Central sensitisation is associated with the depression of

spinal inhibitory mechanisms, through the activation of NMDA receptors. 6, 10, 11

Activation of the NMDA receptors by glutamate in the dorsal horn can contribute to central sensitisation, a mechanism that underpins the process of pain hypersensitivity (hyperalgesia and allodynia in the case of HR) in chronic pain. AMPA receptors are connected physically to NMDA receptors (NMDAR) in the dorsal horn. Normally  $Mg^{2+}$  inhibits NMDAR activity and intracellular kinases are not active. Inflammation in the periphery causes the removal of  $Mg^{2+}$  and NMDA activation. This causes a  $Ca^{2+}$  influx through NMDAR which activates intracellular  $Ca^{2+}$  dependant kinases PKC (protein kinase C), PKA (protein kinase A) and CaMKII ( $Ca^{2+}$ /calmodulin-dependant protein kinase II). These activated kinases phosphorylate the GluR1 and cause the events leading to its insertion into the membrane. The activated PKC phosphorylates GluR2 at Ser880, therefore disrupting the binding of GluR2 to ABP(AMPA-binding proteins)/GRIP(glutamate receptor-interacting protein), causing the internalisation of GluR2. These processes cause AMPARs to switch from being  $Ca^{2+}$  impermeable (GluR2 containing AMPAs) to  $Ca^{2+}$  permeable (GluR2 lacking AMPAs). This causes a further  $Ca^{2+}$  influx and activation of  $Ca^{2+}$  dependant kinases PKC, PKA and CaMKII. This positive feedback loop may be one of the pathways of central sensitisation in inflammation induced chronic pain. 7, 12

Disinhibition of descending inhibitory neurons can also occur, causing pain to be increased. Activation of A-delta primary sensory neurons can cause depression of GABA/Glycine releasing inhibitory neurons. The depression requires NMDA receptor activation and post-synaptic  $Ca^{2+}$  increase. 13

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Modification represents long-lasting changes that alter and distort the normal stimulus-response properties of the pain system. The changes can affect gene expression in ion channels, receptors and transmitters and it can alter connectivity, structure and the survival of neurons. 6 The features of central sensitisation in neurons include the change of nociceptive specific neurons to wide dynamic range neurons that respond to noxious and innocuous stimuli, a progressive increase in responses caused by repeated innocuous stimuli (windup), expansion of the spatial input, and changes that outlast the initial trigger. This can result in spontaneous discharge, an increased receptive field (possible mechanism of secondary hyperalgesia), and an increased responsiveness to innocuous stimulus in the peripheral receptive field (a possible cause of allodynia). 4 A-beta fibres can become sensitised in response to a noxious stimuli. This can result in A-beta fibres producing substance-P and causing the perception of pain, this is a characteristic of central sensitisation. 14, 15

Neuropeptides such as substance-p can diffuse away from its site of release in the dorsal horn and are not inactivated completely by reuptake mechanisms, therefore they are able to excite surrounding excitable neurons/membranes. 7 This could result in the increased excitability and the unlocalised nature of Mrs HR's chronic pain. Genetic alterations that affect the genes involved in sodium channels may cause the perception of pain, even without a noxious stimulus. 2

Glial cells in the CNS can respond to painful stimuli by releasing cytokines. These cytokines have the ability to sensitise post-synaptic receptors and increase the release of neurotransmitters from pre-synaptic neurons. 16, 17

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Microglia and astrocytes can influence neuronal hypersensitivity when activated from their usual quiescent state by injury or inflammation in the CNS. These cells are thought to reduce inhibition, causing an increased pain perception. 7

## **Section C**

Chronic pain is often not well controlled despite the use of analgesics. It is important to use psychological therapies and other techniques such as CBT and relaxation, as a multidisciplinary approach is essential. The focus of treatment for Mrs HR is to reduce her symptoms and pain to a manageable level that is balanced with the negative side effects of her medication. The treatment of chronic pain should be addressed using the biopsychosocial model of pain.

This section of the essay will explain the mechanisms of action of dihydrocodeinine tartrate, its interactions, side effects that are relevant to the patient. HR had co-codamol changed to modified release DHC as she was experiencing disturbed sleep when her co-codamol wore off at night. HR also experienced constipation whilst taking co-codamol. This is a common side effect of opioids due to their action on  $\mu$  and  $\kappa$  opioid receptors on neuronal plexuses in the gut wall.

DHC is a semi-synthetic opioid used for the treatment of chronic pain. DHC is classified as a WHO step two analgesic for managing moderate pain. It is also used as an anti-tussive and as a substitute drug in the treatment of heroin addiction. The side effects of DHC are reduced by using a modified release dosage form. DHC modified release can be used to maintain

therapeutic optimal blood levels for extended time periods and reduce side effects, such as nausea, vomiting and constipation.

A pack of 56 modified release DHC continus tablets (dihydrocodeine tartrate) at 60mg each costs £5. 18. DHC has a half life of three to five hours and is eliminated by metabolism (see appendix A). DHC has a low oral bioavailability due to the fact that it undergoes extensive first pass metabolism. The chemical or metabolites that contribute to the analgesic effect of DHC are unknown.

There are no cautions for DHC use with the patient. There are no significant interactions for the patient taking DHC. Morphine can increase the bioavailability of gabapentin, but this has not been proven in DHC. Alcohol and opioids taken together can cause alcohol-enhanced hypotensive and sedative effects.

Long-term use of opioid analgesics can lead to hyperalgesia. Treatment of opioid induced hyperalgesia include, reducing the dose of opioid or switching therapy and referring to a pain specialist clinic. Opioids can cause drowsiness and may affect the performance of skilled tasks. This could seriously affect the patient as she wouldn't be able to drive to work.

Opioid receptors are coupled to inhibitory G-proteins. Opioid receptor activation inhibits adenylate cyclase and the production of intracellular cAMP. The G-proteins are directly coupled to K<sup>+</sup> channels. The binding of opioids to opioid receptors increases K<sup>+</sup> conductance. This hyperpolarises the cell, making it more difficult to depolarise. The reduced ability of the cell

to depolarise inhibits neuronal voltage-gated  $\text{Ca}^{2+}$  channels and reduces neurotransmitter release.

$\mu$ -receptor stimulation in the raphe magnus of the brain reduces activity in the GABA (gamma-aminobutyric acid) neurons that project to serotonergic neurons in the brainstem. This causes increased firing of descending inhibitory serotonergic neurons that connect pre-synaptically with sensory nociceptive fibres in the dorsal horn of the spinal cord. This inhibits the release of pain causing metabolites, such as substance p, glutamate and nitric oxide from nociceptive neurons. Peripheral nerves contain  $\mu$ -receptors and activation of these by an opioid antagonist reduces the sensitivity to painful stimuli, especially in inflammatory pain.

DHC can cause dependency and is subject to abuse, but it is rare as DHC does not give the euphoria that other opioids do. It is vital that opioid treatment is never abruptly withdrawn after long-term treatment, due to dependency and withdrawal side effects.

## **Section D**

Psychological and social factors can be contributory in the development of chronic pain and in turn they can be caused by chronic pain. Approximately 12% of the general population suffer from chronic pain and an estimated 119 million working days were lost in 2007 due to back pain alone. It can have a detrimental effect on physical and psychological health, daily life, employment, and finances of the person affected. Chronic pain can have a negative impact on friendships and family life and it can be a considerable burden to the healthcare system and the economy. Chronic pain has a major

impact on the wider economy; the total cost of back pain alone was £12.3 billion in 2000.

HR risks losing her job, as she finds it difficult to cope with her pain at work. This is causing her a great deal of emotional distress and results in her sacrificing her hobbies and social time to focus on her work. Work related factors can increase acute and chronic musculoskeletal pain, especially in females. Patients with chronic pain may have perceptions and beliefs about their work which can act as an obstacle to their recovery. Although HR has a stressful job, she finds that it gives her a purpose, as her goals in life are career focused. Working causes HR's pain to increase and results in her being unable to relax and enjoy a social life. This is likely to cause increased stress and its negative consequences. Physical stress and tension from prolonged computer work can prolong chronic pain. The distress exacerbates or complicates the pain, preventing natural healing.

Patients experiencing chronic pain are more likely to have psychopathology than the general population. Pain can promote depression and likewise depression can promote pain. The number of cases where depression is accompanied by pain is between 15-100%. Depression and intensity of pain are significant risk factors in the development of chronic pain. Females are more likely to have pain and depression and have a low response to treatment. HR's chronic pain and its associated symptoms could have a negative effect on her relationship with her husband and friends.

Excess negative thinking or catastrophising about pain and the fear of movement or reinjury are important factors in the development of chronic

pain and its associated disability. HR has little control over her pain. Patients who have control of their pain and associated symptoms are better able to cope with chronic pain and resulting disability than those who are passive to a threat or believe they do not have control. Distraction from pain can be beneficial for the patient as they focus less on the pain experience therefore less pain is perceived. Being able to predict the effects of pain with relative certainty can help a patient deal with their chronic pain. It is vital for the patient to know the aetiology of their pain so that they are less worried and concerned, as this allows the patient to cope better.

Avoidance of activities and fear of causing further pain can be detrimental in chronic pain, whilst in acute pain they are vital for recovery. The patient may become anxious, therefore reducing her pain threshold and tolerance, causing pain to increase in intensity. A belief that activity may worsen the initial injury can result in avoidance of activities. This can stop rehabilitation and lead to physical de-conditioning, causing further pain and disability. This is a self-stoking cycle. The fear of pain can be more disabling than pain itself in some patients.

Patients with neck pain may have a changed pattern of motor control, whereby they use their painful muscles less and use their accessory neck muscles more. Thus causing physical de-conditioning of their postural cervical region muscles and increasing the pain experienced.

Cognitive coping strategies can affect a person's perception and tolerance of pain sensitisations. The avoidance-endurance model of chronicity of pain can be applied to Mrs HR. After her injuries causing acute pain the patient may

have minimised her thoughts about the pain and maintained a positive mood, thus having a suppressive behaviour. Mrs HR may have overdone movements, exercise and her work which caused muscular hyperactivity. Overtime this may have contributed significantly to her chronic pain and its increasing intensity.

## **Conclusion**

The pain system has multiple pathways, with numerous synaptic junctions, complex networks of local and remote controls acting at each junction all with a capacity for neuroplastic change. Pharmacological treatments alone do not always suffice in the management of such a mutli-factorial condition and therefore treatment requires a truly holistic multidisciplinary approach to treat not only the pain but the psychological, social and economic issues of chronic pain.

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