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Central Mechanisms of Pain in Orofacial Pain Patients: Implications for Management

Running title: Central sensitisation in orofacial pain

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Abstract

Background: Central sensitization (CS) is a form of neuroplasticity characterized by changes in the neural sensitivity, responsiveness and/or output that are not contingent on peripheral input nor activity dependent. CS is characterized by activation of unmyelinated C-fibers resulting in a cascade of events at molecular and cellular levels which eventuate into generation of synaptic currents at rest. CS therefore, contributes to heightened generalized pain sensitivity, further complicates the process of reaching a diagnosis, and increases the possibility of treatment failure.

Body: Trigeminal nerve is the main sensory supplier of the anterior part of the head, including the intraoral structures. Primary afferent nociceptors of the trigeminal nerve and low threshold mechanoreceptors synapse with wide dynamic range (WDR) neurons in the pons. This multifaceted network of nerve interactions which is further complicated by the modulatory circuits that can suppress or heighten the activity of WDR neurons is one of the main contributors to CS.

The importance of CS in orofacial pain disorders is emphasized in the context of chronic pain development. As for all chronic pain conditions, it is crucial to consider the biopsychosocial aspects of chronic orofacial pain in managing this diverse group of conditions. This review highlights current understanding of the biopsychosocial model and central mechanisms contributing to the pathogenesis of chronic orofacial pain.

Keywords: central sensitisation, orofacial pain, temporomandibular disorders

Introduction

In order to adequately diagnose and appropriately manage orofacial pain conditions, a fundamental understanding of pain neurophysiology is required. Peripheral and central mechanisms are involved in the etiology and pathophysiology of orofacial pain conditions. Whereas peripheral mechanisms are important in acute and inflammatory-based orofacial pain conditions, central mechanisms are predominantly involved in the causation of chronic orofacial pain conditions. The intervening sections will discuss pain transmission pathways of the head and neck and will review central pain processing and central sensitization.

Central sensitization (CS) can be defined as the exaggerated or amplified response of the central nervous system (CNS) to peripheral nociceptive and sensory stimuli ^{1,2}. This amplified response and sustained hyperexcitability contribute to the development of persistent pain and may manifest as hypersensitivity to pain, allodynia, spontaneous pain, referred pain, and pressure hyperalgesia ^{1,3,4}. CS is considered a form of neuroplasticity and at a neurophysiological level, is first initiated by a brief burst of C-fiber activity followed by nociceptor activity that induces prolonged excitability of dorsal horn neurons ⁵.

Our understanding of CS in orofacial pain conditions has gained significant recent attention especially with specific reference to chronic orofacial pain conditions. The most well-studied of the chronic orofacial pain disorders are temporomandibular disorders (TMD). In TMD, CS contributes to heightened generalized pain sensitivity following isometric contraction of the muscles of mastication ^{6,7}. A proportion of patients with TMD and other chronic orofacial pain conditions have a tendency to focus negatively on their distress through catastrophizing, and as a consequence, suffer from more severe forms of anxiety and often do not respond as well to conventional treatments ⁵. The influence of CS as it pertains to other less well-investigated orofacial pain categories such as myofascial pain, neurovascular pain, and neuropathic pain will be reviewed in the succeeding sections.

This review will address central mechanisms of pain in orofacial pain conditions. CS will be integrated into a biopsychosocial framework for these conditions and implications for the management of orofacial pain conditions will be presented.

Pain Transmission Pathways

In the most parsimonious classification, the events in basic pain perception are divided into transduction, transmission, modulation and perception ⁸. During the transduction phase, noxious stimuli generate action potentials. The action potentials are then transmitted along neurons and then modulated

at synapses under the influence of transmitter substances. The final result is the perception of pain triggered by the noxious stimulus⁸. The pain pathways therefore, collectively form a system for detection and localisation of noxious stimuli that may cause tissue injury enabling a protective response by integrating primitive spinal reflexes, avoidance behaviour and complex emotional responses⁹.

Nociceptors are free nerve endings that have high threshold and customarily, only respond to noxious stimuli. Based on their physiology and function, nociceptors are divided into mechanoreceptors and polymodal nociceptors. The former transfers a well localized, sharp pain sensation through stimulation of thin myelinated A δ -fibers, while the latter stimulates unmyelinated slow-conducting C-fibers to transfer diffuse pain as well as mechanical stimuli¹⁰. It is noteworthy that C-fibers transfer a wide range of activation thresholds (hence the name polymodal): while some respond to a spectrum of noxious stimuli, others are more specific to stimuli type and/or threshold¹¹.

Upon stimulation of nociceptors, an inhibitory postsynaptic potential (IPSP) and an excitatory postsynaptic potential (EPSP) are generated and summated in the axon hillock¹². Although several levels of central and peripheral nervous systems are involved in pain transmission, a balance of IPSP and EPSP is crucial for pain transmission. The action potential is propagated along the neuron and onto the dorsal horn of the spinal cord. The signals are then transferred to the higher brain (CNS). Signals are generally transmitted along the ascending and descending pathways. The ascending pathways transmit sensory information from the body via the spinal cord to the CNS and the descending pathways carry efferent output from the brain to the reflex organs.

The primary sensory pathway of the anterior part of the head, including the intraoral structures is composed of the three main branches of the trigeminal nerve, namely ophthalmic, maxillary, and mandibular branches. The myelinated fibers that innervate the head and neck area include A- β and A- δ . Most A- β fibers are low threshold mechanoreceptors which respond to light mechanical stimuli (e.g., touch), and muscle stretch and tension (e.g., proprioception). The myelinated A- δ and unmyelinated C-fibers terminate as free nerve endings in the head and neck area and respond to noxious stimuli. The difference in threshold has resulted in the generalization that the A- β fibers are touch sensors, while the A- δ and C terminals are nociceptors. The neurons of the trigeminal nervous system are mainly pseudounipolar, and with the exception of proprioceptive afferent neurons whose cells bodies are in the mesencephalic trigeminal nucleus, the remaining cell bodies of trigeminal neurons lie in the trigeminal ganglion¹³. The neurons then travel to the trigeminal nucleus which is divided into subnucleus oralis (uppermost part), subnucleus interpolaris (middle part), and the subnucleus caudalis (the lowermost part)¹⁴. Once the nerve fibers enter the pons, they are considered to be in the CNS as the trigeminal nuclei are considered to be the equivalent of the dorsal horn for orofacial pain. The trigeminal nuclei are where the

first interface between the peripheral nociceptors and CNS occurs. The majority of the pain fibers, and most importantly, the wide dynamic range (WDR) neurons synapse in the subnucleus caudalis. WDR neurons receive sensory input from both the low threshold mechanoreceptors and primary afferent nociceptors. Furthermore, modulatory circuits can suppress or activate WDR activity through the several receptors and ion channels on the cell membrane of WDRs. This entangled network of nerve interactions is a major contributory factor to the complexity of head and neck pain diagnosis and management.

Central Pain Processing and Modulation

Substance P (SP) is a neuropeptide, released from the afferent nerve endings and is involved in nociception and inflammation¹⁵. In response to the release of SP, platelets and immune cells release inflammatory mediators (e.g., prostaglandins, histamine, 5-hydroxytyramine (5-HT), cytokines, and bradykinins) at the site of injury¹⁵. These are the main contributors to peripheral sensitization and mediate experiencing static hyperalgesia which is reflected in increase in spontaneous firing of afferent fibers, and augmented sensitivity to non-noxious stimuli at the site of injury¹⁶. Peripheral sensitization is a defense mechanism that averts the risk of repeated injury through warning the individual of tissue damage. In addition to the chemical modulators discussed above, the expression and activity of voltage gated ion channels may also be affected by nerve injury^{17,18}.

A decline in the activity of nociceptors and the afferent activity to the dorsal horn and the consequent resolution of the static hyperalgesia are expected to occur within a reasonably short span of time⁵. In the case of intense inflammatory response and/or neuronal damage, a central process may occur that increases the risk of sensitization and loss of inhibitory effects of A- δ fibers, thus these fibers may begin signaling pain. This state is referred to as dynamic mechanical allodynia and signifies an increase in the central release of excitatory mediators (e.g., glutamate) and production of nitric oxide¹⁶.

In persistent pain conditions, and downstream to the aforementioned signaling pathways, lies the activation of the mitogen-activated protein kinases (MAPK) cascade which contributes to heightened pain sensitivity through synthesis of proinflammatory/ pronociceptive mediators¹⁶. Given that different MAPK pathways are differentially activated under nociceptive and neuropathic pain, their expression can be used to differentiate between these conditions^{16,19,20}. Thereby, changes in expression of MAPK pathways are considered the last steps in altering the phenotype of nociceptive cells from normal to a pathologic state²¹.

As mentioned above, CS is a form of neuroplasticity that is defined by the *International Association for the Study of Pain* as “increased responsiveness of nociceptive neurons in the CNS to their

normal or subthreshold afferent input”²². The definition implies that CS is a change in the neural sensitivity, responsiveness and/or output and is not contingent on peripheral input nor activity dependent. Although activation of A- δ fibers is considered the hallmark of CS by some, C-fibers are traditionally thought to initiate the process through modulating alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors, and consequently allowing an influx of Ca⁺ ions through ion channels^{23,24}. Further increase in the intracellular level of Ca⁺ in response to glutamate and SP results in phosphorylation of the N-methyl-D-aspartate (NMDA) receptor, which in turn eventuates into generation of synaptic currents at rest²⁵. In subjects who had sustained spinal injury, new growths of A- δ fibers were noted in the lamina I and II of the dorsal horn, which is usually occupied by C-fiber^{26,27}. In addition to these new growths, the ability of A- δ fibers to secrete SP suggests a potential role for these neurons in pain transmission^{28,29}.

Our perception of pain is further complicated by the influence of intense emotions. In major fight or flight situations, such as in stress after major injury, noxious stimuli may not elicit any pain but when anticipated, pain perception may be heightened. The periaqueductal gray matter (PAGM) of the midbrain is innervated by the serotonergic neurons and is a major part of the descending inhibitory system, involved in pain modulation³⁰. Predictably, stimulation of PAGM has been shown to cause a delayed response to noxious stimuli in rats³¹. However, PAGM is not the sole brainstem pain pathway modulation center. In brief, three main networks, namely ascending (sensory), descending (motor), and modulatory are involved in emotion processing in the brainstem. Current evidence suggests that while signal integration and modulation occur along all the levels of brainstem, thalamus, hypothalamus and cerebral cortex host the most complicated network interaction allowing phylogenetically older pathways in the brainstem (involved in fixed-action pattern responses), to be regulated by evolutionarily newer rostral regions³⁰. Here, in the interface between pattern responses and new information lies an important component of CS. However, this close network integration and the multifaceted nature of the pain and emotion pathways suggest that our current knowledge of this interface is conceptual and would benefit from further revision and investigation.

Central Sensitization in Orofacial Pain

The importance of CS in orofacial pain disorders is emphasized in the context of chronic pain development³². Persistent nociceptive input that may be a result of trauma, inflammation or other noxious stimuli may lead to so-called “stimulus-dependent” or “activity-dependent” CS through the mechanisms detailed earlier in this review. Additionally, the spontaneous action potentials in A- and/or C-fibers characterizing neuropathic mechanisms can initiate and maintain CS³³. When unabated, the

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persistent input can engage other complex mechanisms of pain modulation, such as loss of inhibitory interneurons, alterations within ion channels and neurotransmitter receptors, culminating in centrally-mediated pain, which is independent of stimulus or activity^{1,34,35}. Among the clinical manifestations of CS are the presence of poorly defined and/or spontaneous pain (location, source, or specific inciting factors), hyper-responsiveness to noxious stimuli (hyperalgesia) intensified by repeated stimulation, and pain caused by low intensity stimuli (mechanical or thermal allodynia)^{34,36}. In addition to these patterns of pain, CS is associated with alterations in sleep and mood, such as anxiety and depression, which are important aspects of patient presentation and part of the Axis II assessment in the setting of biopsychosocial approach to TMD^{37,38}. The presence of these characteristics of CS in patients presenting with orofacial pain frequently correlates with cases that are more difficult to treat and often require multidisciplinary care and centrally-acting pharmacotherapeutics for effective management³⁸.

In 2016, Kosek *et al.* proposed the addition of another mechanistic descriptor for chronic pain states, namely, nociplastic pain, to the already existing nociceptive and neuropathic pain descriptors³⁹. This definition aids the description of chronic pain states involving apparently normal tissues characterized by hypersensitivity (both with clinical findings and psychophysical alterations), but where both objective nociceptor activation cannot be demonstrated and criteria for neuropathic pain cannot be met. The official definition for nociplastic pain, now accepted by the IASP, is “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.” This term replaces “dysfunctional pain” whose nonspecific nature and lack of mechanistic hypothesis, in addition to the potential stigma implied with the term “dysfunctional” demonstrates its inadequacy as a descriptor. The concept of nociplastic pain also arises from the inference that, in these chronic pain states which do not fall under nociceptive or neuropathic definitions, altered nociception and sensitization may be the underlying mechanism as shown by alterations in quantitative sensory testing (QST), sensory evoked potentials and functional magnetic resonance imaging. Its clinical importance lies in the possibility that CNS changes in nociceptive processing occurs in these states, similarly to those of neuropathy, and this may be supported by the observation that patients with the characteristics under this descriptor are more responsive to therapies targeting central processes than peripheral processes. Pain disorders which fulfill this definition include fibromyalgia, complex regional pain syndrome and irritable bowel syndrome, the so-called central sensitivity syndromes. It is also important to note that patients may present with a combination of nociceptive pain, neuroplastic pain and nociplastic pain. These combinations are now commonly called ‘mixed’ pain⁴⁰.

Nociplastic pain is also distinct from “pain of unknown origin,” previously known as idiopathic pain. As such, it is not intended to be a diagnostic term nor to be used interchangeably with CS, although the commonality of sensitization may lead to the use of this term to describe clinical disorders in which CS is evidenced, provided the conditions for the term are satisfied ^{39,41}.

When addressing CS in clinical settings, one should also be aware of the distinction between CS and the central sensitivity syndromes (CSS). CS, as previously described, is a phenomenon which refers to the neuroplastic changes that lead to temporal summation, hyperalgesia, and allodynia, and altered descending inhibition mechanisms, all of which may be a part of an important adaptive protective process to permit healing of damaged tissue in the acute setting. Because altered CNS pain processing is a hallmark feature of CS, an important tool for analyzing the presence of CS is Quantitative Sensory Tests (QST) which uses calibrated sensory stimuli to quantify detection thresholds which may be noxious or innocuous and is of value in evaluating orofacial pain ^{36,42}.

Furthermore, CS is involved in chronic and dysfunctional (nociplastic) pain states with influence from psychosocial parameters, thus characterizing a maladaptive process ¹. CSS or chronic overlapping pain conditions (COPC) refers to a group of diseases and disorders with a shared pathophysiological mechanism, namely CS, and overlapping signs and symptoms of chronic and widespread pain, along with sleep disorder, fatigue and cognitive dysfunction ^{7,43}. This distinction is important especially when considering neuropathic pain disorders such as trigeminal neuralgia in which CS contributes to, and can sustain, the characteristic pain pattern, and signs and symptoms following insult to the nervous system; however the underlying pathophysiology is the presence of a lesion or disease of the somatosensory nervous system ⁴⁴. As such, neuropathic pain disorders should be ruled out when considering a diagnosis of CSS.

Temporomandibular Disorders

A diagnosis of TMD is characterized by pain involving the temporomandibular joint and surrounding and supportive structures, including masticatory muscles. There is however, a large spectrum for the clinical presentation and etiologic factors involved in TMD. Studies have suggested underlying alterations in genes involved in neurotransmission and inflammation in patients with more chronic, centrally-mediated TMD ^{43,45}. In an attempt to describe the heterogeneity of TMD, studies found that TMD patients could be clustered into three different groups with respect to pain intensity and psychological distress in that the third group represents those with higher pain intensity and higher psychological distress ⁴⁶. A majority of patients with TMD present with comorbid pain conditions such as headache/migraine, neck pain, joint pain, and lower back pain ⁴⁷. Approximately one-quarter of patients

with TMD meet diagnostic criteria for fibromyalgia which is characterized by widespread pain, and less than 20% of TMD patients present with pain that is localized to the orofacial region ^{47,48}. These characteristics are consistent with the inclusion of TMD in CSS/COPCs ^{7,43,49}. QST in COPC, including TMD, demonstrate widespread hypersensitivity, hyperalgesia and allodynia in both painful and pain-free sites throughout the body, reinforcing the evidence of CS in the pathophysiology of these disorders ^{42,50,51}. As such it is important to recognize when these phenomena are present, in order to adequately address the patient's pain with respect to the overriding etiology, whether it be peripheral, central, or a combination of both.

Burning Mouth Syndrome

Another example of CS in orofacial pain disorders is burning mouth syndrome which can be subdivided into three groups. The first is characterized by peripheral neuropathic pain with hypoesthesia upon thermal QST, demonstrated in association with small fiber neuropathy of the tongue and impairment of the A- δ cool afferents primarily. The second group is characterized by a mix of peripheral and central mechanisms. The third group consists of a more centrally-mediated process with evidence of heat pain hyperalgesia and allodynia in addition to alterations in dopamine levels and the presence of additional psychosocial comorbidities such as anxiety and depression ^{52,53}. The distinction of these subgroups is important clinically because treatment strategies differ depending on the underlying mechanisms, in that topical treatments are likely to be effective in patients with predominantly peripheral-driven processes while targeting of the dopamine-opioid axis would be a more appropriate approach in patients with centrally-driven processes ⁵³.

Biopsychosocial Aspects of Central Sensitization

The long-held convention that chronic pain conditions such as orofacial pain disorders are solely attributed to a direct biological or pathological cause, and that psychosocial factors are not directly implicated in their pathophysiology has long become obsolete. As for all chronic pain conditions, the biopsychosocial model is the model currently used to explain the orofacial pain field. This model has proven crucial to our understanding of the pathophysiology of a litany of orofacial pain conditions and has provided valuable insights into the complexity of pain processing. This model is characterized by an integrated synergistic dynamic process in which there is interplay between psychological, social and biological factors (Table 2). There exists a definite reciprocation of the resultant psychological effects on the propagation of the existing biological disease process. Social factors such as access to care, employment, socioeconomic status, skepticism, family support and psychological factors such as anxiety,

depression, somatoform disorders, anger, catastrophizing, self-efficacy, and fear avoidance comprise the main components of this model ^{2,54}.

An oversimplified case-specific example of the biopsychosocial influence on CS of an orofacial pain condition is presented here. A patient with classical trigeminal neuralgia experiences several daily episodes of paroxysmal excruciating sharp-shooting pain for several seconds that is easily triggered by mastication. Utilizing this model with specific reference to CS in classical trigeminal neuralgia patients; (i) the biological factor is one of frequent neuropathic pain during pain episodes, (ii) the psychological factors may be catastrophizing and fear avoidance, and (iii) the social effects may be avoiding public social gatherings that involve any kind of eating or drinking. All three aspects of the biopsychosocial model are simultaneously worsening the disease process with significant reciprocal effects. These combined effects have serious implications on self-confidence, contribute to worsening mental health, and exacerbate anxiety and depression ⁵⁵. More so, these effects of fear avoidance cause the patient to have perceived disability and result in them having to constantly disuse (disengage from mastication) from the fear of the intractable pain returning, thus lowering the threshold at which pain is experienced ^{55,56}. This in turn contributes to a chronic state of trigeminal neuralgia whereby in addition to the excruciating short-lived episodes of stabbing pain, the patient experiences a constant low-grade dull throbbing background of muscular or neuropathic pain ^{57,58,59}. This entity has been referred to as *classical trigeminal neuralgia with concomitant persistent facial pain* ⁵⁷. Furthermore, longer episodes of paroxysmal pain have been reported in this subset of trigeminal neuralgia patients ⁵⁷. In addition, pain thresholds are lowered to a level whereby pain is triggered in the absence of the usual nociceptive stimuli ¹. This vicious cycle drastically reduces treatment outcomes and contributes to persistent disease. Therefore, this aforementioned example highlights how biopsychosocial factors can feed into CS and how chronic background pain can be a product of CS in trigeminal neuralgia ^{60,61}.

An often unrecognized social factor that is overlooked by clinicians in the management of chronic orofacial pain patients is negative reactions by friends, family, and other healthcare providers who show a great deal of scepticism about their condition. This disbelief and scepticism stems from the perception that, in the absence of physical/objective signs, this perceived “invisible” pain disorder is contrived for attention purposes ². These social experiences have negative psychological effects that propagate anxiety and depression, and contribute to worsening biological effects. Therefore, as part of the management protocol, it is important to raise awareness and keep family members informed about the nature and etiology of orofacial pain conditions.

Provided the stringent clinical time constraints, the implementation of thorough comprehensive psychosocial assessments are not feasible in modern day clinical settings. Fortunately, effective ultra-brief

screening instruments for psychosocial comorbidity exist and have been specifically formulated for orofacial pain. One such instrument is the screening version of the *Diagnostic criteria for TMD (DC/TMD) Psychosocial Axis (Axis II) Assessment*⁵⁴. With this rapid screening tool, the clinician can perform a biopsychosocial assessment using a limited number of questions and based on the number of positive responses, a referral for a detailed evaluation can be made⁵⁴.

Several researchers have explored the etiology of recalcitrant persistent orofacial pain cases and it has become abundantly clear that external psychosocial factors play a significant role in treatment failure. Consequently, the incorporation of a cognitive-behavioral approach centered on the biopsychosocial model can feasibly be undertaken by adopting established comprehensive and multidisciplinary pain management programs (PMPs). In addition to standard conventional treatments, these PMPs may include physiotherapy, occupational therapy and clinical psychology input and offer access to paced exercise programs, adjunctive biofeedback, stress reduction, distraction, reappraising thoughts, breathing control, relaxation, and other mindfulness and cognitive-behavioral strategies^{37,54,62-64}. These programs have significantly improved outcomes for chronic pain patients including orofacial pain patients and, compared to conventional therapy, PMPs are cost-effective, improve patients' function and result in reductions in medication use and additional treatments, and importantly, patients incur significantly fewer visits to dental healthcare providers^{2,37,62,64,65}. Moreover, self-reported improvements on pain and depression outcomes have been reported^{37,62-64,66}. Importantly, a 2006 randomized controlled trial (RCT) demonstrated the short- and long-term efficacy of brief PMPs in the management of TMD⁶⁶. In this RCT, in addition to standard therapy, TMD patients were randomized to either four sessions of cognitive-behavioral therapy (CBT) (n= 79) or stand-alone conventional approaches (n= 79). TMD patients who received CBT had greatly improved outcomes at 12 months in terms of pain intensity, masticatory jaw function, and in depression symptom severity scores.

Conclusions

The preceding sections illustrate the complexity of pain processing and highlight our current understanding of central mechanisms of orofacial pain. It is evident that further research is needed in the setting of a biopsychosocial model to better enhance our understanding of the etiology of orofacial pain conditions. Importantly, research geared in the light of a biopsychosocial model should aim to venture beyond TMD research and include various other chronic orofacial pain conditions. Furthermore, to ensure maximum treatment success in the management of chronic orofacial pain patients, a thorough understanding of the biopsychosocial model is required and aspects of this model should be incorporated in the assessment and management of certain patients.

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Table 1. Disorders Associated with Central Sensitivity Syndrome

Mood Disorder
Posttraumatic stress disorder
Orofacial/Head and Neck Pain Disorders
Tension-type headache
Migraine
Chronic myofascial pain (TMD)
Burning mouth syndrome
Persistent dentoalveolar pain
Persistent idiopathic facial pain
Occlusal dysesthesia
Halitophobia
Gastrointestinal Pain Disorders
Primary dyspepsia
Irritable bowel syndrome
Genitourinary Pain Disorders
Endometriosis
Primary dysmenorrhea
Vulvodynia/vulvar vestibulitis
Painful bladder syndrome/interstitial cystitis
Chronic prostatitis/chronic male pelvic pain
Musculoskeletal Pain Disorders
Fibromyalgia
Complex regional pain syndrome
Myofascial pain syndrome
Primary chronic neck pain
Primary low back pain
Movement Disorders
Periodic limb movement disorder
Restless legs syndrome
Other
Multiple chemical sensitivity

* Adapted from Yunus (2015) ⁶⁷

Table 2. Components of the Biopsychosocial Model

Biological Factors
Neurophysiology
Tissue pathology
Genetics
Social Factors
Access to medical care
Employment
Socioeconomic status
Social stigma
Skepticism
Social learning
Operant conditioning
Family support
Psychological Factors
Anxiety
Depression
Somatoform disorders
Anger
Catastrophizing
Self-efficacy
Fear avoidance
Hypervigilance
Perceived control