REPORT 3 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-17)
Neuropathic Pain as a Disease
Resolution 912-I-16
(Reference Committee K)

EXECUTIVE SUMMARY

Objective. This report considers whether neuropathic pain should be recognized as a distinct disease state.

Methods. English-language reports on studies using human subjects were selected from a MEDLINE search of the literature from 2005 to August 2017 using the search terms "neuropath*," in combination with "pain," and "pathophysiology," "chronic," and "pain as a disease." A total of 103 articles were retrieved for analysis based on their ability to supply new information about the pathogenesis of chronic and neuropathic pain, as well as viewpoints on whether chronic (including neuropathic) pain can or should be considered as a disease in its own right. Medical dictionaries were consulted for definitions of disease and related terms.

Results. Understanding of the human pain experience has evolved over time. Although a detailed understanding of the neuroanatomy underlying the perception of noxious stimuli (nociception), exists, neuroimaging studies have identified several brain regions that are activated during the pain experience, dubbed the "pain matrix;" many of the same regions are also activated during various emotional and behavioral responses. Chronic pain is now recognized as an integrative sum of nociceptive input and factors related to cognition, mood, and context, as well as individual biologic, psychologic and social factors and various co-morbidities. Many "diseases" are accompanied by persistent pain, and chronic pain itself has been described by some as a disease. With respect to neuropathic pain, many different types of neural lesions and systemic diseases trigger neuropathic pain symptoms, which include various positive, negative, and evoked symptoms. Much of the thinking about chronic pain as a disease has been driven by the results of neuroimaging studies. Neuropathic pain also is characterized by adaptive cellular and functional changes which appear to persist after healing of the original injury. Based on neuroimaging, cross sectional studies of structural and functional changes accompanying chronic pain, including neuropathic pain, support clear differences compared with both normal conditions and the presence of acute nociceptive pain. It remains unclear what the cause and effect relationships might be, or whether such brain alterations should be viewed primarily as an adaptive response to continuing nociceptive input.

Conclusion. Evaluating neuropathic pain as a distinct disease state would be best deliberated by a group of multi-specialty experts involved in the evaluation and treatment of pain who could more deeply focus on the topic and consider all of its ramifications. At the 2016 Interim Meeting the House adopted a resolution directing the American Medical Association (AMA) to convene a Federation-based pain care task force (Policy D-160.922). This task force is in the process of being formed, and the Council believes that it is a more appropriate body to address this issue in a comprehensive manner.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 3-I-17

Subject: Neuropathic Pain as a Disease (Resolution 912-I-16)

Presented by: Robert A. Gilchick, MD, MPH, Chair

Referred to: Reference Committee K (L. Samuel Wann, MD, Chair)

Resolution 912-I-16, "Neuropathic Pain as a Disease," introduced by the American Academy of Pain Medicine at the 2016 Interim Meeting and referred to the Board of Trustees, asked:

> That our American Medical Association recognize neuropathic pain as a disease state with multiple pathophysiological aspects requiring a range of interventions to advance neuropathic pain treatment and prevention.

METHODS

English-language reports on studies using human subjects were selected from a MEDLINE search of the literature from 2005 to August 2017 using the search terms "neuropath*," in combination with "pain," and "pathophysiology," "chronic," and "pain as a disease." A total of 103 articles were retrieved for analysis based on their ability to supply new information about the pathogenesis of chronic and neuropathic pain, as well as viewpoints on whether chronic (including neuropathic) pain can or should be considered as a disease in its own right. Medical dictionaries were consulted for definitions of disease and related terms.

BACKGROUND

The Council previously examined the issue of neuropathic pain on two occasions. In 2005, the Council reviewed the neurobiology of nociceptive and neuropathic pain, and the definition, classification, common causes, diagnostic approach, and pharmacologic management of neuropathic pain.[1] In 2010, the Council reviewed more recent findings about how neural damage, which is the signature precipitating event for the development of neuropathic pain, provokes multiple responses in nociceptive pathways that generate and amplify pain.[2] Such responses include peripheral and central sensitization, ectopic activity in pain carrying fibers, neuronal cell death, disinhibition, altered gene expression, neuron sprouting, neuronal plasticity and modified neural connectivity.[2] Some discussion was devoted to whether such changes, which can eventually persist in the absence of ongoing noxious stimuli, should be considered maladaptive and warrant consideration as a disease. The Council did not specifically endorse that viewpoint, concluding in part, that the clinical value of viewing chronic or neuropathic pain as a disease was not established. This report responds to the specific request that our AMA, through Council evaluation and deliberation by the House of Delegates, recognize neuropathic pain as a disease state. It is already established that neuropathic pain is characterized by "multiple pathophysiologic aspects" and

Action of the AMA House of Delegates 2017 Interim Meeting: Council on Science and Public Health Report 3 Recommendations Adopted, and Remainder of Report Filed.

requires a treatment approach that differs from that applied to chronic nociceptive and inflammatory pain.

RELEVANT DEFINITIONS

Pain

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[3] This definition acknowledges that pain is a conscious experience involving interpretation of (painful) sensory input that is influenced by emotional, pathological, and cognitive factors, as well as previous pain experiences.

Nociceptive Pain

Nociceptive pain is caused by tissue injury generating pain through the primary somatosensory nervous system via a process involving activation of peripheral nociceptors, transduction, transmission, modulation and perception of noxious stimuli. Nociceptive pain can be acute, subacute or chronic, may be complicated by inflammation, and may be visceral or referred in origin.

Chronic Pain

Chronic pain has been variously defined. The definition used by the Centers for Disease Control and Prevention in developing its guideline on the use of opioids in chronic noncancer pain is based on the International Association for the Study of Pain (IASP) definition:

> "Ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury healing, more than 3 to 6 months, and which adversely affects the individual's well-being"[4]

Neuropathic Pain

Neuropathic pain was re-defined by the IASP in 2012 as "pain initiated or caused by a lesion or disease of the somatosensory system."[5] The basis for this definition is that "neuropathic pain is not a single disease, but a syndrome caused by a range of different diseases and lesions, which manifests as an array of symptoms and signs."

Disease

- An interruption, cessation, or disorder of body function, system, or organ OR a morbid entity characterized usually by at least two of these criteria: recognized etiologic agent(s), identifiable group of signs and symptoms, or consistent anatomic alterations.[6]
- Any deviation from or interruption of the normal structure or function of any body part, organ, or system that is manifested by a characteristic set of symptoms and signs whose etiology, pathology, and prognosis may be known or unknown.[7]

Syndrome

The aggregate of symptoms and signs associated with any morbid process, and constituting together the picture of the disease.[7]

Disorder

An illness that disrupts normal physical or mental functions.[6]

EVOLUTION OF PAIN THEORY

Initial investigation and understanding of pain focused on describing the specific somatosensory pathways involved in pain processing.[8] Nociception is the perception of noxious stimuli and represents an alarm signal mediated by specialized primary afferent (sensory) neurons that respond

to sufficiently intense thermal, mechanical, or chemical stimuli, transduce these stimuli into electrical activity, and transmit signals via well-defined pathways in the central nervous system. Cell bodies of the primary afferent neurons are located in dorsal root ganglia and the spinal sensory nucleus of cranial nerve V; bifurcated axonal processes are distributed to the periphery for detection, and to the spinal cord to transmit information centrally. Aδ fibers (thinly myelinated) carry a well-localized "first" pain of sharp, pricking quality. C fibers (unmyelinated) carry a poorly localized "second" pain of dull and persistent or burning quality. Muscle and deep tissue nociceptor stimulation produce aching or cramping type pain. There are several sub-populations of primary afferents that differ in their axon diameter, response to stimuli, neurophysiologic and neurochemical characteristics and targets in the dorsal horn of the spinal cord.[9] When local inflammation ensues, certain features of the nociceptive response are modified and magnified to aid healing and repair.

In the spinal cord, peripheral pain-carrying primary afferent terminals synapse on (second order) neurons within the superficial lamina of the dorsal horn, which ascends to form the spinothalamic tract and spinoreticular system. The former transmits information about acute pain (location, intensity, quality) through the thalamus to the somatosensory cortex and the latter is involved with autonomic and affective reactions to pain. The dorsal horn is not a simple relay station but is subject to "gating" by local interneurons with inhibitory and excitatory influences, as well as descending influences from the midbrain and higher centers.[10]

Secondary spinal projection neurons transmit nociceptive information to brainstem regions, including the rostral ventral medulla and periaqueductal gray (PAG); this information is further modulated in the brainstem, relayed to the thalamus, and then transmitted to the cortex where it is interpreted as pain. Several cortical regions are involved in pain processing, including the primary somatosensory cortex, secondary somatosensory cortex, insular cortex, prefrontal cortex, and motor cortex.[11]

The Pain Matrix

Although a detailed understanding of the neuroanatomy of nociception exists, neuroimaging studies have identified several brain regions that are activated during the "pain experience." This pattern of neural activation has been posited to represent an array of interrelated brain regions integral to human pain perception and response or colloquially representing the "neurosignature of pain."[l2-15] An extensive neural network (dubbed the "pain matrix") is accessed during the processing of nociceptive input including the primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices and the thalamus; subcortical areas (e.g., brain stem, PAG, hypothalamus, amygdala, hippocampus, and even the cerebellum) also are involved in the pain experience.[15-19] Thus, modulation of the primary nociceptive stimulus occurs within the spinal cord where noxious stimuli are just part of the overall sensory input, in response to descending neuronal influences, and at numerous supraspinal levels affecting the discriminative, emotional, and cognitive aspects of pain.[4,10,20]

Neuroimaging studies have shown that many brain regions activated by nociceptive stimuli also are activated during various emotional and behavioral responses, and that non-nociceptive events or inputs (e.g., loss of a loved one, social exclusion) can produce pain-like experiences.[21-23] These types of findings have informed a conceptual three-tiered hierarchical model of the human pain experience based on nociception (1st tier), conscious perception subject to cognitive and attentional modulation and the triggering of somatic reactions (perceptive-attentional, 2nd tier), and consideration of how individual factors and characteristics (including psychological factors and emotional context) influence pain and the memory of that experience (reappraisal-emotional, 3rd

tier).[24] Brains regions involved in the second and thirds tiers can either inhibit or facilitate nociception in a descending fashion.

The Biopsychosocial Model of Chronic Pain

Pain is an individual and subjective experience, recognized as an integrative sum of nociceptive input and factors related to cognition, mood, and context, as well as individual variables such as genetics and sex. Chronic pain and patient outcomes are influenced by individual biologic, psychologic and social factors and various common comorbidities (Figure 1).[25,26] Brain regions involved in the pain matrix are involved in many other sensory, motor, cognitive, and emotional functions and a reciprocal relationship exists between chronic pain and mental health disorders. Neural pathways that involve pain, depression and anxiety overlap and likely have important biological interactions that are not well understood.[27] Chronic pain induces disturbances in mood (reactive depression or anxiety), impaired coping (often with catastrophization), and other processes which can worsen pain and pain-related distress and lead to fear-avoidance behaviors. Pain patients also have much higher premorbid or comorbid psychosocial concerns, mental health disorders and cognitive distortions that influence the pain experience and drive pain-related distress. Individuals who observe other people's suffering often experience a subjective enhancement of their own pain suffering.[28] Thus, the pain experience is influenced by various cognitive, emotional, and environmental factors affecting brain function.[29] Chronic pain is a multidimensional experience that, like other chronic conditions has multiple contributors, including psycho-behavioral ones. Effective management often demands a multidisciplinary assessment and treatment plan that identifies and addresses all the components of the individual's pain experience.

IS CHRONIC (OR NEUROPATHIC) PAIN A DISEASE?

Many "diseases" are accompanied by persistent pain including cancer, human immunodeficiency virus infection, osteoarthritis/rheumatoid arthritis, lower back injury, headache, degenerative spine disease, fibromyalgia, diabetes, post herpetic neuralgia, etc. However, when considering whether neuropathic pain is a disease, it is important to note that the question of whether chronic pain should be considered a disease is not a new concept.

In 2001, the IASP and the European Federation of IASP Chapters adopted the following declaration:

> "Pain is a major healthcare problem worldwide. Although acute pain may reasonably be considered a symptom of disease or injury, chronic and recurrent pain is a specific healthcare problem, a disease in its own right."

The landmark 2011 report by the Institute of Medicine on Relieving Pain in America concluded that:

> Chronic pain can be a disease in itself. Chronic pain has a distinct pathology, causing changes throughout the nervous system that often worsen over time. It has significant psychological and cognitive correlates and can constitute a serious, separate disease entity.[30]

In 2016 Vardeh et al noted:

> The past few decades have witnessed a huge leap forward in our understanding of the mechanistic underpinnings of pain, in normal states where it helps protect from injury, and also in pathological states where pain evolves from a symptom reflecting tissue injury to become the disease itself. [31]

Neuropathic Pain

With respect to neuropathic pain, many different types of neural lesions and systemic diseases trigger neuropathic pain symptoms (e.g., diabetes, post-herpetic neuralgia, radiculopathies, stroke, spinal cord injury, chemotherapy, certain surgeries, alcohol misuse, vitamin deficiencies, heavy metal toxicity, and many other causes and triggers).[32] Signs and symptoms characteristic of neuropathic pain include spontaneous "positive" (gain of function) signs (e.g., paresthesias, burning, shooting or shock-like pains), "negative" (loss of function) signs (e.g., numbness, weakness, hypoalgesia, decreased tendon reflexes) and certain stimulus-dependent or evoked signs (e.g., allodynia, hyperalgesia) (Figure 2).[33] Diseases causing neuropathic pain vary substantially in terms of anatomical location and cause; depending on the cause, individual patients exhibit similar clinical characteristics, but not all symptoms that are commonly associated with neuropathic pain. Two prominent neuropathic pain symptoms across causes are allodynia (pain induced by normally innocuous stimuli) and hyperalgesia (increased pain in response to noxious stimuli) (see below).

Debate on Chronic Pain as a Disease

The field of pain medicine, the Institute of Medicine and some clinicians and researchers have proposed that chronic pain should be considered a disease; others continue to see pain primarily as a symptom of disease.[30,34-39] Much of the thinking about chronic pain as a disease has been driven by neuroimaging studies, and structural/functional changes observed in animal models of chronic pain and/or neural injury. It has been proposed that because some unique changes accompany neural injury, chronic pain with a neuropathic component should be considered in a distinct fashion.[40]

Neuroimaging. An extensive literature base exists on using various brain imaging techniques in patients with chronic pain, including neuropathic pain; most studies have been cross-sectional. A comprehensive review is beyond the scope of this report. A critical review of more than 100 brain neuroimaging reports identified neural correlates of chronic pain associated with various diseases (i.e., osteoarthritis, irritable bowel syndrome, back pain, fibromyalgia) and demonstrated distinctions from images associated with acute nociceptive pain.[41] Patients suffering from chronic pain also exhibit dysfunction in descending inhibition of pain, less gray matter in the thalamus and prefrontal cortex with more gray matter loss in patients with neuropathic components; differences in various measures of brain neurochemistry also have been demonstrated.[41] Subsequent studies extended these findings to other chronic pain conditions (pelvic pain, complex regional pain syndrome, diabetic peripheral neuropathy, phantom limb pain) demonstrating changes in gray matter density in multiple cortical regions, as well as the amygdala and hippocampus.[14] What remains unresolved is to what extent altered structure, function and neurochemistry represents a "disease" or are simply neuroplastic adaptive processes in response to ongoing nociceptive input, or reflect the consequences of pain, common co-morbid conditions, medications, or altered lifestyles in patients with chronic pain.[42]

Cellular and Functional Changes. Adaptive and persistent cellular and functional modifications also have been used to support the concept that neuropathic pain, in particular, is a chronic disease. As described in the previous Council report, neural injury provokes a host of neuroplastic and neuroimmune responses which become drivers of neuropathic pain, some of which also are common to persistent nociceptive/inflammatory pain.[2,43-46] These include:

- peripheral sensitization of nociceptors related to altered trafficking of ion channels. Peripheral sensitization decreases the threshold for activation and augments normally painful stimuli (primary hyperalgesia) and triggers the development of spontaneous (ectopic) activity in primary afferent neurons;
- central sensitization, characterized by increased spontaneous activity, expansion of receptive fields, and a decreased threshold to primary afferent inputs into the dorsal horn.

This ultimately enhances the function of neurons and circuits in nociceptive pathways via increased membrane excitability, increased synaptic efficacy, and reduced inhibition. It manifests as mechanical allodynia and secondary hyperalgesia;

- changes in the phenotype of low threshold sensory fibers (Aβ) that are normally activated by touch, pressure, and vibration, to one whereby they can generate sensations of pain or tenderness;
- a pathological triad of reciprocal interactions among neurons, immune cells, and glial cells with glia activation and release of proinflammatory mediators that contributes to both peripheral and central sensitization; and
- disinhibition resulting from an imbalance of excitatory and inhibitory influences at the spinal cord level, and descending facilitation from the brain stem and higher centers.

DISCUSSION AND COMMENT

Recognition of chronic pain as a disease may lead to increases in resources, education, and priority, but considerable attention has already been devoted to the burden of chronic pain in the United States, and a National Pain Strategy has been developed.[47]

A disease, by definition, requires a set of "characteristic signs and symptoms." Chronic pain is:

> complex, affecting individuals physically, mentally, socially and spiritually. This results in a common symptomatic and functional spectrum of physical, cognitive, psychological and behavioral effects. Decreased physical functioning coupled with little hope for effective treatment often results in a downward spiral of depression, distress, anxiety, and sleep problems, which lead to impaired social functioning and family relationship that all increase perceived pain.[48]

Some of these consequences may be explained by common neural substrates or reciprocal interactions and may not be considered unique to chronic pain because they can accompany any chronic condition that causes substantial distress.

With neural injury or repetitive nociceptive stimuli, remodeling of the nervous system and alteration in gene expression occurs. Such changes reflect neuroplasticity that impacts pain in the peripheral and central nervous system, leading to increased excitability within pain circuits and generating peripheral and central sensitization, which underlie the phenomena of hyperalgesia, allodynia, and the spread of pain to adjacent uninjured regions (secondary hyperalgesia). Based on neuroimaging research, cross sectional studies of structural and functional changes accompanying chronic pain, including neuropathic pain, support clear differences compared with both normal conditions and the presence of acute nociceptive pain, but it remains unclear what the cause and effect relationships might be, or whether such brain alterations should be viewed primarily as an adaptive response to continuing nociceptive input. Do these phenomena fulfill the requirement for the presence of "characteristic signs and symptoms?" Does it make sense to consider an altered pain response as a symptom that can logically define pain as a disease?

With respect to pain management and relieving the burden of suffering among patients with chronic pain, it would seem that wider adoption of the biopsychosocial model of pain management should be the most important goal, with attention to reducing pain, restoring function, cultivating well-being and improving quality of life. This requires identifying and addressing psychosocial contributors and emphasizing active over passive modalities. For neuropathic pain, diagnostic and management approaches are different; preferred initial pharmacological interventions are

antiepileptic and antidepressant drugs. Several interventional approaches are available but psychobehavioral approaches can be more challenging in patients with neural injury.[2]

CONCLUSION

The topic of neuropathic pain as disease would be best deliberated by a multi-specialty group of experts involved in the evaluation and treatment of pain that could more deeply focus on the topic and consider all of its ramifications. At the 2016 Interim Meeting the House of Delegates adopted a resolution directing the AMA to convene a Federation-based pain care task force (Policy D-160.922). This task force is in the process of being formed and the Council believes that it is a more appropriate body to address this issue in a comprehensive manner.

RECOMMENDATION

The Council on Science and Public Health recommends that the following statement be adopted in lieu of Resolution 912-I-16 and the remainder of this report be filed:

That the Federation Task Force on Pain Care evaluate the relative merits of declaring neuropathic pain as a distinct disease state, and provide a recommendation to the Council on Science and Public Health. (Directive to Take Action)

Fiscal Note: Less than $500

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Figure 1. Biopsychosocial Context of Pain

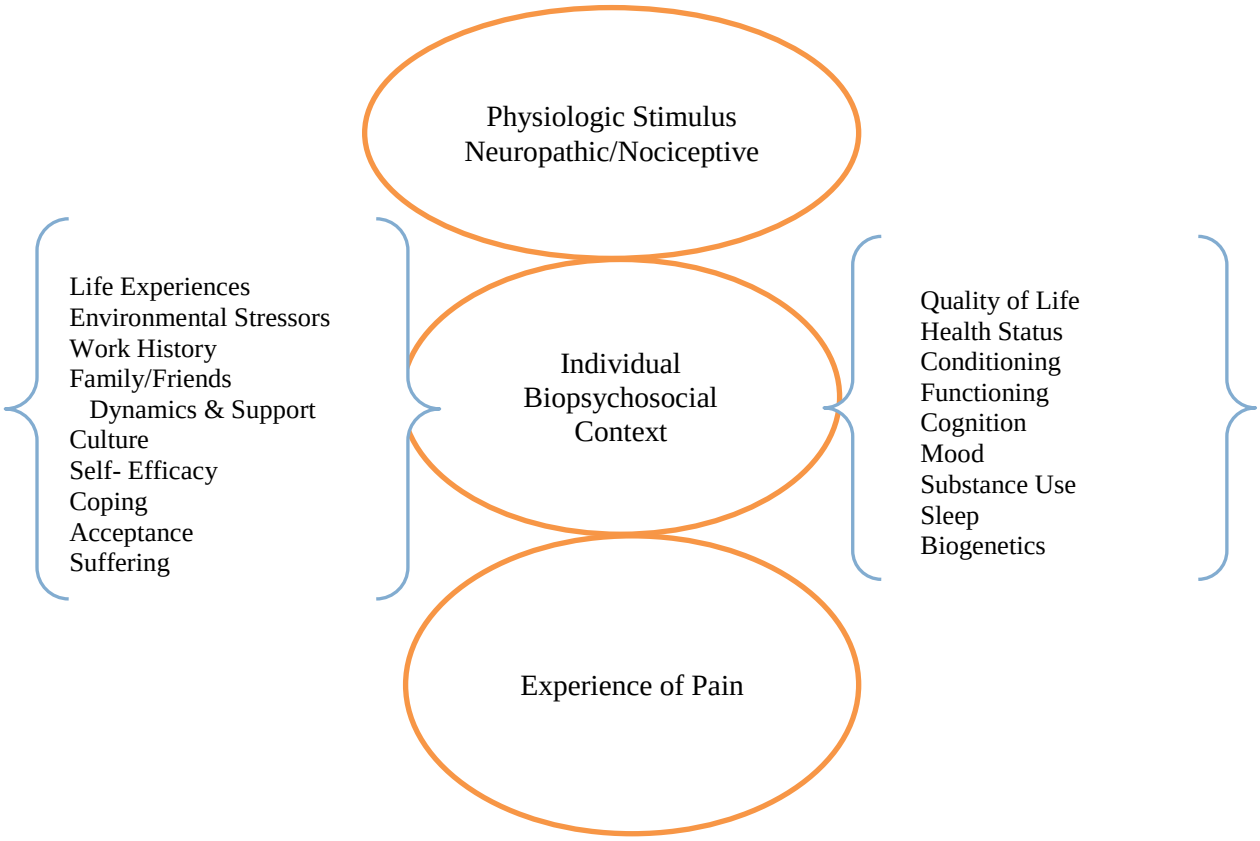

Figure 2. Signs and Symptoms Characteristic of Neuropathic Pain