REPORT 5 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-10)
Maldynia: Pathophysiology and Non-pharmacologic Treatment
(Resolution 525, A-08)
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. The Council previously examined the issue of neuropathic pain, particularly the role of pharmacotherapy for symptomatic management. This report addresses recent findings on the pathogenesis of neuropathic pain. Per the request of Resolution 525 (A-08), attention is devoted to the concept that development of maladaptive pain (maldynia) justifies its classification as a disease. Additionally, the scope of non-pharmacologic approaches employed in patients with maladaptive pain is discussed.

Methods. English-language reports on studies using human subjects were selected from a MEDLINE search of the literature from 1995 to March 2010 using the search terms "maldynia" or "neuropath*," in combination with "pain," "pathophysiology," "diagnosis," and "treatment." In addition, the Cochrane Library was searched using the term "pain," in combination with "neuropathic" or "neuropathy'" and "psychologic," "stimulation," "spinal cord," "acupuncture," or "hypnosis." A total of 406 articles were retrieved for analysis. Articles were selected for their ability to supply information about the pathogenesis of neuropathic pain, and modes of therapy beyond pharmacologic intervention. When high-quality systematic reviews and meta-analyses were identified, they formed the basis for summary statements about treatment effectiveness. Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the American Pain Society (www.ampainsoc.org), American Academy of Pain Medicine (www.painmed.org), American Academy of Pain Management (www.aapainmanage.org), and the American College of Occupational and Environmental Medicine (www.acoem.org).

Results. Nociceptive pain is an alarm signal mediated by specialized primary sensory neurons that respond to sufficiently intense thermal, mechanical, or chemical stimuli and transmit signals via well-defined pathways in the central nervous system. Nociceptive pain is triggered and maintained by the presence of noxious stimuli. When neural tissues in the peripheral or central nervous system are directly damaged or become dysfunctional a different sequence of events unfolds. Under these conditions pain can manifest and eventually persist in the absence of typical nociceptive generators. Such pain is maladaptive in the sense that it occurs in the absence of ongoing noxious stimuli, does not promote healing and repair, and responds poorly to conventional pain medications. According to this viewpoint "pain becomes the disease process itself" and is termed maldynia. This condition (as defined) can result from neural injury or inadequately managed persistent nociceptive stimuli.

Conclusion. Neural damage to either the peripheral or central nervous system provokes maladaptive responses in nociceptive pathways that generate and amplify spontaneous pain. Multiple processes are involved, including peripheral and central sensitization, ectopic activity, neuronal cell death, disinhibition, altered gene expression, and abnormal sprouting and cellular connectivity. A series of neuro-immune interactions underlie many of these mechanisms. Imaging studies have shown that several pain conditions associated with neural injury are characterized by functional, structural, and chemical changes in the brain. As such, maldynia is a multidimensional process that may warrant consideration as a chronic disease not only affecting sensory and emotional processing, but also producing an altered brain state, based on both functional imaging and macroscopic measurements. The absolute clinical value of this definition is not established.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 5-A-10

Subject: Maldynia: Pathophysiology and Non-pharmacologic Treatment (Resolution 525, A-08)

Presented by: C. Alvin Head, MD, Chair

Referred to: Reference Committee E (Brooks F. Bock, MD, Chair)

Resolution 525 (A-08), "Neurobiology of Neuropathic Pain," introduced by the American Academy of Pain Medicine at the 2008 Annual Meeting and referred to the Board of Trustees, asks:

> That our American Medical Association prepare a report based on current scientific literature which addresses the pathophysiology of maldynia as a neurobiological disease; and
>
> That such report address the therapeutic scope of practice for non-pharmacological therapies for maldynia including interventional and non-interventional modalities.

BACKGROUND

The Council previously examined the issue of neuropathic pain, particularly the role of pharmacotherapy for symptomatic management.[1] This report addresses recent findings on the pathogenesis of neuropathic pain. Per the request of Resolution 525 (A-08), attention is devoted to the concept that development of maladaptive pain (maldynia) justifies its classification as a disease. Additionally, the scope of non-pharmacologic approaches employed in patients with neuropathic pain is discussed. Various complementary and alternative medicine approaches (e.g., acupuncture, meditation, hypnotherapy, chiropractic, aromatherapy, etc.) have been used in patients with acute and persistent pain, but have not been systematically studied in neuropathic pain and are not further evaluated. A glossary of terms used in this report appears in the Appendix.

METHODS

English-language reports on studies using human subjects were selected from a MEDLINE search of the literature from 1995 to March 2010 using the search terms "maldynia" or "neuropath*," in combination with "pain," "pathophysiology," "diagnosis," and "treatment." In addition, the Cochrane Library was searched using the term "pain," in combination with "neuropathic" or "neuropathy'" and "psychologic," "stimulation," "spinal cord," "acupuncture," or "hypnosis." A total of 406 articles were retrieved for analysis. Articles were selected for their ability to supply information about the pathogenesis of neuropathic pain, and modes of therapy beyond pharmacologic intervention. When high-quality systematic reviews and meta-analyses were identified, they formed the basis for summary statements about treatment effectiveness. Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the American Pain Society (www.ampainsoc.org), American Academy of Pain Medicine (AAPM) (www.painmed.org),

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Action of the AMA House of Delegates 2010 Annual Meeting: Council on Science and Public Health Report 5 Recommendations Adopted, and the Remainder of the Report Filed.

American Academy of Pain Management (www.aapainmanage.org), and the American College of Occupational and Environmental Medicine (www.acoem.org).

CLASSIFICATION OF PAIN

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[2] 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. Historically, the classification of pain has focused on whether pain was acute or chronic, or the symptoms warranted designation as a chronic pain syndrome with attendant comorbidities and biopsychosocial implications. Alternatively, pain has been classified: (1) based on its location (focal, multi-focal, generalized, and referred); (2) in a temporal fashion (acute, intermittent, or continuous); (3) based on its site (headache, neck or back pain) and etiology (cancer or noncancer; visceral, neurogenic); and (4) based on severity (duration, frequency, intensity). These categories retain some clinical usefulness but lack a cohesive pathophysiologic basis. Because of this existing taxonomic array, the AAPM has proposed categorizing pain on a neurobiologic basis as: *eudynia* (nociceptive pain) from the Greek for "good pain" or *maldynia* (maladaptive pain) from the Greek for "bad pain."

Nociceptive pain is an alarm signal mediated by specialized primary sensory neurons that respond to sufficiently intense thermal, mechanical, or chemical stimuli and transmit signals via well-defined pathways in the central nervous system. Nociceptive pain is triggered and maintained by the presence of noxious stimuli. When local inflammation ensues, certain features of the nociceptive response are modified and magnified to aid healing and repair.

When neural tissues in the peripheral or central nervous system are directly damaged or become dysfunctional, a different sequence of events unfolds. Under these conditions pain can manifest and eventually persist in the absence of typical nociceptive generators. Such pain is maladaptive in the sense that it occurs in the absence of ongoing noxious stimuli, does not promote healing and repair, and responds poorly to conventional pain medications. According to this viewpoint which has largely been advanced by AAPM and other proponents in the pain medicine community, "pain becomes the disease process itself" (maldynia).[3-6] Furthermore, this condition can be viewed as *primary* when the pain is initiated or caused by a primary lesion or dysfunction in the nervous system (definition of neuropathic pain) or can be considered as *secondary* when it results from persistent, inadequately relieved nociceptive stimulation. Therefore, the term maldynia (as defined) encompasses more than neuropathic pain *per se*, and when the term "maldynia" is used in this report, its use corresponds to this definition; otherwise, the more common terms of neuropathic or nociceptive pain are employed. Additionally, although nociceptive pain and maldynia have distinct features, they coexist in certain chronic pain states (e.g., failed back syndrome).

The remainder of this report focuses on contemporary knowledge about the neurobiologic basis of pain and tries to place this in perspective of the premise of Resolution 525 (A-08), namely that the pathophysiology of maldynia constitutes the basis for claiming such pain as a disease process unto itself.

NEUROBIOLOGY OF PAIN

Nociceptive Pain

Primary afferent sensory neurons are responsible for processing temperature, touch, proprioception, and pain sensations. Neurons that transmit information about potentially damaging (noxious) stimuli are known as "nociceptors." Although eudynia is an acute normal physiologic response to tissue injury that serves as a warning or protective mechanism, certain diseases may generate recurrent or ongoing noxious stimuli and can produce persistent nociceptive pain (e.g., osteoarthritis, cancer).

Cell bodies of primary afferent neurons are located in dorsal root ganglia (DRG) situated outside the central nervous system (CNS) and the spinal sensory nucleus of cranial nerve V. Acute nociceptive pain is normally evoked only by stimuli that are sufficiently intense to activate primary afferent Aδ (lightly myelinated) and C (unmyelinated) fiber nociceptors. These pseudounipolar neurons have bifurcated axonal processes, one innervating peripheral cells, tissues, and organs for detection of noxious stimuli, and one that enters the spinal cord to transfer information to the CNS. Nociceptors comprise numerous varieties, either responding to a specific noxious stimulus, or more commonly exhibiting polymodal responses to chemical, heat, severe pressure and/or mechanical stimuli.[7] Functionally, they transduce temperature, chemical, or mechanical forces via voltage-gated Na channels (Na_V) and transient receptor potential channels (TRPV1; TRPA1) into electrical activity.[7] Under certain conditions, impulses can travel distally along the peripheral axon of the nociceptor, resulting in the local release of neuropeptides that can produce vasodilation, increased vascular permeability, localized edema, and white blood cell infiltration (neurogenic inflammation).

Aδ and C-fibers terminate in a highly organized, topographic pattern in the dorsal horn of the spinal cord. Several well characterized chemical signals mediate pain transmission in response to incoming noxious stimuli. The outermost thin marginal layer (Lamina I) comprises small neurons that are largely nociceptive-specific (NS) and have small receptive fields. Lamina II (also known as the *substantia gelatinosa*) principally contains interneurons involved in processing input from fibers conveying noxious stimuli. Ascending projections from Lamina I mediate the affective-motivational and to a certain extent sensory-discriminative aspects of human pain. Lamina V receives convergent input from both low- and high-threshold sensory fibers (innocuous and noxious) with large receptive fields comprising so-called wide dynamic range (WDR neurons); central projections from this area play a larger role in somatic responses and sensory decoding. Primary afferent terminals in the dorsal horn are subject to several local dampening influences, including voltage-gated Ca^{2+} channels and endogenous gamma amino butyric acid (GABA), opioid, and cannabinoid receptors, as well as prominent descending inhibitory influences.

Dorsal horn neurons ascend to form the spinothalamic tract and spinoreticular pathways that relay noxious information to the thalamus and higher cortical centers. Ascending pain signals from dorsal horn cells rely to a large extent on rapid synaptic transmission mediated by the excitatory amino acid glutamate, acting on N-methyl-D-asparate (NMDA) receptors. Although the anatomical tracts that convey primary nociceptive signals centrally are well characterized, pain is a complex, multifactorial, subjective experience comprising sensory, cognitive, and emotional components. Accordingly, based on imaging studies, an extensive neural network (dubbed the "pain matrix") is accessed during processing of nociceptive input. This network includes the primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices and the thalamus; subcortical areas (e.g., brain stem and amygdala) also are involved in the pain experience.[8-11] 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.[8,12,13]

Inflammatory Pain. With tissue injury sufficient to provoke an inflammatory response, various mediators (e.g., cytokines, chemokines, kinins, tumor necrosis factor-α [TNF_{α}]) can directly activate nociceptors and trigger both peripheral sensitization of nociceptors and central sensitization of dorsal horn neurons (see below). Such changes involve alterations in neural structure and function and are associated with various chronic pain states. With peripheral and central sensitization, low threshold stimuli that are normally innocuous become painful, and noxious stimuli trigger more intense and prolonged pain responses. Heightened pain sensitivity also may develop in adjacent uninjured areas.[14,15] Like (typical) nociceptive pain, inflammatory pain disappears after healing of the initial tissue injury and resolution of the inflammation; however, in chronic inflammatory disorders such as rheumatoid arthritis, the pain persists as long as inflammation and noxious stimuli are evident.[16]

Neuropathic Pain

Neuropathic pain is defined by the International Association for the Study of Pain as "pain initiated or caused by a primary lesion or dysfunction in the nervous system." Some have argued that use of the term "dysfunction" makes this definition vague and unacceptably broad and that it may be more appropriate to define neuropathic pain as pain caused by a lesion of the peripheral or central nervous system (or both), manifesting with sensory symptoms and signs.[17] Peripheral neuropathic pain results from lesions to the peripheral nervous system caused by mechanical trauma, metabolic diseases, neurotoxic chemicals, infection, or tumor invasion.[18] Central neuropathic pain most commonly results from spinal cord injury, stroke, or multiple sclerosis.[19] See Table 1 for the common causes and types of neuropathic pain states.

At least 4 million individuals suffer from peripheral neuropathic pain, most commonly peripheral diabetic neuropathy (PDN) and postherpetic neuralgia (PHN); epidemiological studies on the prevalence of neuropathic pain indicate a population incidence as high 5%.[21-23] After spinal cord injury, pain develops in approximately 60% to 70% of patients.[24,25] Even more patients may suffer from secondary maldynia.

Neuropathic Pain Symptoms. Neuropathic pain typically comprises a combination of distinct sensory symptoms that coexist in various combinations with motor and autonomic signs; both positive and negative sensory symptoms may be manifest (see Table 2).[18,26] Neuropathic pain exhibits a heterogeneous presentation, including persistent or paroxysmal shock-like or burning pain, tingling, paresthesias, and hypoesthesia.

Despite the fact that neuropathic pain can develop from many different causes, patients demonstrate a similar constellation of symptoms across five domains (Table 3). Burning pain is most commonly associated with PHN, and paroxysmal pain is most commonly associated with trigeminal neuralgia.

Diagnosis of neuropathic pain is based on medical history; review of systems; physical neurological examination; functional motor assessment; sensory examination; psychological testing; and appropriate laboratory studies, including blood and serologic tests, magnetic resonance imaging, and electrophysiologic studies.[27,28] Different scales and questionnaires have been developed in an attempt to discriminate between neuropathic pain and non-neuropathic pain, and

various tools are available to screen for neuropathic pain.[29] More detailed information on the assessment of pain, quantitative sensory testing, and measures of neuropathic pain is available.[30-37]

Certain other persistent pain conditions (e.g., fibromyalgia, interstitial cystitis, irritable bowel syndrome) lack identifiable noxious stimuli, inflammation, or detectable damage to the nervous system.[5] In such conditions, pain is associated with amplification of nociceptive signals within the CNS and altered sensory processing that can sometimes be detected by functional imaging.[38,39] These dysfunctional pain syndromes share some features with neuropathic pain, namely reduced pain thresholds (sensitization) and the presence of diffuse pain.[38]

Processes Common to Inflammatory and Neuropathic Pain

Inflammatory and neuropathic pain share some common features, namely peripheral and central sensitization and neuro-immune interactions.

Peripheral Sensitization and Primary Hyperalgesia. With tissue injury and inflammation, nociceptors are exposed to substances that either directly activate or sensitize them (e.g., ATP, H+, prostaglandin E, bradykinin, pro-inflammatory cytokines, neurotrophic factors).[4,9] These mediators activate intracellular transduction pathways, prompting an increase in the production and membrane insertion of transducer and voltage-gated ion channels. Peripheral nerve damage causes an expression and clustering of specific Na_V channels at injury and neuroma sites, and in neighboring uninjured afferents, some of which appear to be necessary for the expression of neuropathic pain.[40-42] Further evidence supporting the important role of voltage-gated Na channels in neuropathic pain is the fact that point mutations affecting the function of the Na_V 1.7 channel leads to painful inherited neuropathies (i.e., primary erythromelalgia and paroxysmal extreme pain disorder).[40]

Peripheral sensitization decreases the threshold for nociceptor activation, augments normally painful stimuli (primary hyperalgesia), and triggers spontaneous depolarization in primary afferents (ectopic activity). With peripheral nerve injury, neurotrophic factors also can be transported in a retrograde direction, thereby affecting DRG and dorsal horn cells.

Central Sensitization, Secondary Hyperalgesia, and Mechanical Allodynia. Peripheral nociceptor hyperactivity induces secondary neuroplastic changes in their spinal cord targets, leading to increased spontaneous activity, expansion of receptive fields, and a decreased threshold to subsequent afferent inputs in dorsal horn neurons (central sensitization).[43] Central sensitization is a major pathophysiological mechanism common to persistent inflammatory, neuropathic, and dysfunctional* pain based on activity-dependent synaptic plasticity. Central sensitization ultimately enhances the function of neurons and circuits in nociceptive pathways via increased membrane excitability, increased synaptic efficacy, and reduced inhibition.

Enhanced co-release of glutamate and peptide neurotransmitters (e.g., substance P, calcitonin gene-related peptide) from nociceptors enables the activation of NMDA receptors, which increases intracellular calcium concentrations in dorsal horn neurons. Nerve injury increases the spinal cord expression and/or activity of voltage- and ligand-gated ion channels, peptide receptors, and neuro-immune factors that drive dorsal horn neuron hyperexcitability. Nerve injury also modifies gene expression, prompting nociceptive specific neurons (Lamina I) to take on the characteristics of

*As defined by Costigan and Woolf, certain persistent pain conditions (e.g., fibromyalgia, interstitial cystitis, irritable bowel syndrome) lack identifiable noxious stimuli, inflammation, or detectable damage to the nervous system and have been termed "dysfunctional."[5]

WDR (as in Lamina V). When these neurons are subjected to repeated stimulation, they respond with an exaggerated response (wind-up).

At the cellular level, stimulation thresholds are reduced, neuronal activity in response to noxious stimuli is increased, peripheral receptive fields of some spinal cord neurons are expanded, and neurons in related spinal segments become hyperexcitable.[27] Clinically, central sensitization manifests as pain sensitivity beyond the site of tissue damage or inflammation (secondary hyperalgesia). Similar synaptic changes occur in structures involved in the emotional aspects of pain such as the amygdala, anterior cingulate gyrus, and prefrontal cortex, which may represent a substrate for long-term cognitive and mood changes that are learned and retained in patients with persistent pain.[44,45]

Neuro-Immune Interactions. It is now recognized that reciprocal interactions among immune surveillance cells, glial cells, and neurons are responsible for triggering and maintaining many of the pathophysiologic changes and functional characteristics of neuropathic pain.[46] Peripheral interactions play a role in amplifying pain responses during inflammation, and both peripheral and central processes play key roles after neural injury

PSYCHOLOGICAL ISSUES IN PATIENTS WITH PERSISTENT PAIN

It is important to note that a number of psychological issues are paramount when discussing disease processes or the treatment of patients with persistent pain, as is the case for other chronic medical conditions. A number of studies have evaluated the role of psychosocial and psychological factors with regard to pain severity, functioning, and disability in patients with persistent pain.

Physical symptoms are common in patients suffering from major depression. Approximately 30-60% of patients with depression report moderate to severe pain symptoms at diagnosis.[47,48] The reverse trajectory also is true; chronic pain from a long-term medical condition doubles the incidence of depression and one-third to more than one-half of patients with persistent pain presenting to pain clinics have major depression.[49] Depression in patients with chronic pain is associated with greater pain intensity, pain persistence, a decrease in self-efficacy, lower perceived social support, higher self-report of physical disability, pain catastrophizing, and observable pain behaviors. [50-52] Optimized antidepressant therapy followed by a pain self-management program results in substantial improvement in depression and more moderate reduction in pain severity and disability in patients with chronic musculoskeletal pain.[53] Anxiety and avoidance beliefs also are related to poorer function in patients with chronic pain.[54]

The extent of pain catastrophizing shapes the experience of acute and persistent pain and predicts pain-related outcomes.[55] Pain-related catastrophizing is broadly conceived as a "set of exaggerated and negative cognitive and emotional schema that emanate during actual or anticipated pain."[56] Collectively, this behavior is characterized by a tendency to magnify the threat and to feel more helpless in the context of pain, as well as ruminating about pain before, during and/or after a painful encounter.[55] Negative thought patterns such as catastrophizing are closely related to outcomes of perceived pain intensity and mood in persons with persistent pain. Attention, expectation, and reappraisal are important cognitive modulators of pain.[56] Pain-related cognitions and emotional decision-making abilities contribute to the variance in how patients describe their pain intensity.[9]

Thus, specific psychological traits or experiences affect an individual's response to pain and suffering. These include fear, attention and vigilance to pain, catastrophizing and worry, avoidance of pain-inducing activity, mood disorders, anger and hostility, self-denigration, differences in the

ability to achieve control in the face of distress and disability, and the ability to comprehend the factors exacerbating pain.[57] These psychological factors must be addressed in managing patients afflicted with persistent pain.[58]

PATHOPHYSIOLOGY OF MALDYNIA—MECHANISMS OF NEUROPATHIC PAIN

Most of the knowledge about the molecular and cellular mechanisms following neural injury has been derived from animal models (e.g., ligature, axotomy, chronic constriction, spinal cord lesions). Some corroborating data are available from human models, and insights have been gained from human imaging and genetic studies. It is increasingly apparent that the pathophysiologic response to neural injury involves a triad of reciprocal interactions among neurons, immune cells, and glial cells. With nerve damage, several mechanisms are triggered that affect primary afferent receptors, their axons and cell bodies, components of the inflammatory/immune response, central neurons and their connections, and glial cells. Many of these processes are adaptive, such as removal of cellular debris, neural changes to counteract a loss of input, promoting survival of neurons, synaptic remodeling, and remyelination.[59,60] However, many responses are clearly maladaptive, including peripheral and central sensitization, ectopic impulse generation, phenotypic switching in pain-carrying fibers, neuronal loss, disinhibition, altered gene expression, neuronal plasticity, and apparent structural reorganization in the brain.[61] The essential elements of these maladaptive responses are further explained in the following sections.

Ectopic Impulse Generation

Peripheral sensitization can trigger spontaneous depolarization (ectopic activity) in primary afferents, which become a driver for central sensitization. Ectopic activity also can develop along damaged axons (neuromas) and from the sprouting of sympathetic efferents, which may form rings or "baskets" around dorsal root ganglion cells. Sympathetic-sensory coupling is thought to contribute to inflammatory pain, the pain associated with complex regional pain syndrome, diabetic neuropathy, post-herpetic neuralgia, phantom limb sensations, and other conditions.[8,62-64] With peripheral nerve injury, ectopic discharges also may originate in the DRG neuron causing antidromic stimulation of afferent C fibers, the release of mediators, and (neurogenic) inflammation at the periphery.

Deafferentation (loss of normal input due to nervous system injury) also produces hyperresponsiveness and spontaneous discharges in spinal cord or thalamic neurons.[17] Processes associated with degeneration of neighboring axons within the spinothalamic tract, such as inflammation, may trigger spontaneous activity in residual intact neurons that act as a "central pain generator" after spinal cord injury.

Low-Threshold Aβ Fiber-Mediated Pain

A role for low-threshold (Aβ) sensory fibers that are normally activated by touch, pressure, vibration, and joint movement is evident after neural injury. In addition to their normal sensory role, these fibers mediate the suppression of nociceptive pain caused by rubbing the affected area (the "gate" control theory), but when nerve injury creates conditions of disinhibition (see below), these fibers develop novel abilities to activate superficial dorsal horn nociceptive projection neurons. Peripheral injury to sensory nerves triggers a regeneration response to aid damaged peripheral neurons in reconnecting with their targets. Such gene-activated growth stimuli also may prompt Aβ fibers to "sprout" into the more superficial layers of the spinal cord (Lamina II). Combined with central sensitization, these adaptations manifest clinically as the ability of stimuli from low-threshold Aβ receptors to generate sensations of pain or tenderness (dynamic mechanical

allodynia).[45,65-68] Thus, as a consequence of peripheral nerve injury, low-threshold input from large myelinated fibers is transferred to nociceptive circuits in the spinal cord.

Disinhibition

Local inhibition in the spinal cord is essential for appropriate encoding of sensory signals. Numerous local spinal inhibitory neurotransmitters (e.g., opioids, cannabinnoids, GABA, neuropeptide Y, adenosine) and also descending systems (e.g., norepinephrine) normally have the capacity to impede the development of hyperalgesia and/or allodynia. Both primary sensory and dorsal horn neurons degenerate over a period of several weeks following peripheral nerve injury.[69] Peripheral nerve injury also provokes a pathologic loss of spinal cord inhibitory neurons, particularly those that release the inhibitory neurotransmitter GABA.[5,70] This process (disinhibition) augments pain transmission. Magnetic resonance imaging (MRI) investigations in patients with chronic neuropathic pain hint that neurodegeneration also may occur in the brain.

Neuro-Immune Contributions

Spinal cord glial cells, such as microglia and astrocytes, play a critical role in the induction and maintenance of neuropathic pain by releasing and responding to powerful neuromodulators, including proinflammatory cytokines and chemokines.

Glial cells. Collectively, glia greatly outnumber neurons in the central nervous system. Subtypes include resident and perivascular microglia, astrocytes, and oligodendrocytes; the latter provide the sheath for central myelinated neurons and are therefore important in the repair of damaged neurons. It is now apparent that glia actively communicate with neurons and contribute importantly to the development of different types of neuropathic pain states.

Microglia play a key role in the response to nervous system injury. These cells are recruited and activated in the vicinity of the central terminals of injured sensory nerve fibers. Activated microglia produce numerous inflammatory mediators (IL-1B, IL-6, TNFα, PGE_2, nitric oxide, and brain derived neurotrophic factor [BDNF]).[47] They also express receptors for numerous substances including purines (ATP), neuropeptides, neurotransmitters, chemokines, and neurotrophic factors.

Glial signaling pathways involve ATP, chemokines, and toll-like receptors (TLRs). ATP-stimulated glia activate pain-projection neurons in the dorsal horn. Neuron-derived ATP activates purinergic ionotropic receptors (P2X4) on microglia, further releasing microglial ATP and BDNF, which modifies (dampens) the inhibitory actions of GABA in spinal lamina neurons; further injection of ATP-activated microglia induces mechanical allodynia.[71,72]

Astrocytes also can modulate neuronal signaling because they completely encapsulate synapses and are in close contact with nerve cell bodies. Like microglia, astrocytes express various functional receptors for neurotransmitters (glutamate, purines, substance P) and a wide range of pattern recognition receptors, like TLRs. When astrocytes are activated, various so called mitogen-activated protein kinases (MAPK) also are activated.[73,74] MAPKs are a small family of evolutionally conserved molecules that play a critical role in cell signaling and gene expression via different signaling cascades.

Cytokines. Cytokines are any of a number of substances (peptides, proteins, glycopeptides) that are secreted by specific cells of the immune system and mediate intercellular communication. In common use, the term "cytokine" has been used to refer to the immunomodulating agents, such as interleukins and interferons.

Chemokines. *Chemo*tactic cyto*kines* (chemokines) represent a family of small, secreted proteins first discovered and normally involved in controlling the migration of white blood cells to inflammatory sites. Neurons, glia, and microglia are able to both synthesize and respond to chemokines.[46,75,76] Chemokines and chemokine receptors also are widely expressed in the nervous system where they help regulate stem cell migration, axonal path finding, and neurotransmission.

Toll-like receptors (TLRs). TLRs are a family of 12 evolutionarily conserved membrane proteins that provide surveillance for invading pathogens. TLRs activate various protein kinases leading to the activation of transcription factor NF-κB, upregulation of interferons, and increased expression of proinflammatory cytokines. Neuropathic pain is substantially reduced when purinergic receptors are blocked or certain TLRs are knocked out.[72,77]

Immune Surveillance and Response Following Neural Injury

In the peripheral nervous system, immune surveillance is performed by macrophages, which identify and clear cellular debris and present surface antigens to activate T-lymphoctyes. Both macrophages and T-lymphocytes communicate via cytokines and chemokines with neurons, oligodendrocytes and Schwann cells, and DRG satellite cells. Macrophages participate in the degenerative response to axonal injury, and immune activation in the injured nerve and DRG appears to contribute to pain hypersensitivity.[46] Microglia function as the macrophages of the CNS and also are strongly activated in the dorsal horn after peripheral nerve injury, close to the central terminals of injured afferents.[78]

Microglial cells respond to, and release, many immune modulators (proinflammatory cytokines and chemokines), activating several signaling cascades that contribute to the induction and maintenance of neuropathic pain by altering neuronal function.[79,80] Additionally, there is reciprocal communication between neurons and glia cells. The actions of inflammatory cytokines synthesized by DRG neurons, as well as by microglia and astrocytes in the spinal cord, contribute to changes in the excitability of nociceptive sensory neurons.[81] Nociceptors respond directly to cytokines, chemokines, and other inflammatory mediators produced in inflamed tissues.[82] Interleukin-1β (IL1β), TNF_{α}, bradykinin, and nerve growth factor elicit action potentials by increasing sodium and calcium currents at the nociceptor peripheral terminal (peripheral sensitization). Chemokines are capable of influencing peripheral sensitization by: (1) directly activating nociceptors; and, (2) along with neurotrophic factors and other inflammatory mediators, by altering the expression and function of the transient receptor potential channels (TRPV1; TRPA1) that transduce noxious stimuli into action potentials.[75] After nerve damage, these same inflammatory mediators are produced by peripheral immune cells and microglia in the spinal cord and contribute to neuropathic pain by activating dorsal horn nociceptive neurons (central sensitization).

After injury, chemokine levels increase in central primary afferent fibers. Their release may either directly stimulate DRG neurons (provoking the release of pain-related neurotransmitters) and/or stimulate neighboring chemokine-expressing neurons. DRG neurons upregulate the expression of chemokine receptors in a reciprocal fashion. Direct administration of chemokines elicits allodynia in animal models.[83] TNF_{α} also stimulates DRG neurons and upregulates the expression of chemokines. Antagonists to chemokines and TNF_{α} prevent or attenuate ongoing neuropathic pain behavior in animal models.[46,84]

Thus, both microglia and astrocytes express various functional receptors that are activated by classical neurotransmitters, neuromodulators, and chemokines. They receive and respond to signals during synaptic transmission and neuroimmune processes that alter their membrane properties and activate gene transcription leading to further pro-inflammatory events. The

contributions of immune cells and glia to the development and the persistence of pain after nerve injury challenge conventional concepts that neurons are primarily responsible for the pathophysiologic changes underpinning the development of neuropathic pain.

GENETIC DETERMINANTS OF PAIN

A substantial minority of individuals who experience neural injury do not develop neuropathic pain. Therefore, it is likely that both environmental and multiple risk-conferring genes influence the development and expression of neuropathic pain in individuals. Based on animal studies, several genes involved in pain perception and modulation have been described.[85] As a baseline, twin studies reveal that genetic factors contribute 20-60% of the variance in nociceptive pain sensitivity.[86,,87] Some rare recessive conditions affecting sodium channels are associated with either pain insensitivity or extreme pain.[85] In addition, Fabry disease, a rare X-linked recessive lysosomal storage disease, may be characterized by burning neuropathic pain that can be difficult to manage. Based on gene association studies, some candidate genes related to pain sensitivity include polymorphisms in the catechol-O-methyltransferase, *mu* opioid receptor, melanocortin-1 receptor, and TRPA1 gene; certain haplotypes of the enzymes involved with tetrahydrobiopterin synthesis also are related to pain sensitivity.[88-91]

NEUROANATOMICAL AND NEUROIMAGING STUDIES

Although animal models have been useful in identifying cellular and molecular changes accompanying neural injury, their predictive value for maldynia is less certain. Brain imaging modalities, including positron emission tomography (PET), single photon emission computerized tomography (SPECT), and functional magnetic resonance imaging (fMRI), have advanced the understanding of pain processing in the human brain. Brain activation in response to nociceptive pain involves six main areas: the primary and secondary somatosensory cortices; the insular cortex, the anterior cingulate cortex, the thalamus, and the prefrontal cortex.[92] Activation in these areas is related to sensory-discriminative aspects of pain, affective-emotional aspects, and cognitive aspects, respectively.

At a macroscopic level using volumetric MRI, significant decreases in gray matter volume and density have been described in patients with chronic neuropathic (back) pain, complex regional pain syndrome, phantom pain, chronic migraine, irritable bowel syndrome, fibromyalgia, and trigeminal neuralgia compared with age-matched control subjects; the magnitude of changes tend to correspond to the duration of symptoms.[93-103] However, the precise nature of these structural changes remains to be determined. Patients with persistent pain frequently have comorbid conditions, including anxiety and mood disorders, altered and more sedentary life-styles, and also are taking various drugs that themselves might be contributing to these measured changes.[97]

PET studies have shown: (1) decreases in brain opioid receptor binding; and (2) reduced thalamic activity and increased brain activity in brain areas associated with the affective/emotional dimensions of pain.[92,105-107] Similar results have been found with the use of SPECT.[108] In patients with evoked allodynia, changes have been observed in the activation of brain structures not usually considered part of the pain matrix (motor, premotor areas; parietal cortex, basal ganglia, and cerebellum). fMRI use enables blood oxygen level dependent signals to detect changes in cerebral activity in patients with neuropathic pain, and this technique allows the study of discriminative sensory, emotional, motivational, and modulatory responses in particular regions of the brain and brain stem.[96,97] fMRI has been used to delineate a comprehensive inventory of brain regions involved in the response to evoked allodynia. During allodynic stimulation, additional brain areas are activated compared with the normal pain network. In one study, subjects who had previously

experienced allodynia, just imagining that touch is painful leads to activation of the anterior cingulate gyrus and prefrontal cortex.[109,110] Evidence of functional plasticity and alteration in basic processes in the brain and brain stem of patients with neuropathic pain have been identified in other imaging studies as well.[111-113] These findings demonstrate that neuropathic pain, like other major neurological and psychiatric diseases, appears to have a widespread impact on overall normal brain function.

MANAGEMENT OF MALDYNIA

Previously, the Council evaluated the role of drug therapy in the symptomatic management of neuropathic pain.[1] Many drugs used in patients with primary maldynia are not classified as analgesics *per se*, including antidepressants, antiepileptic drugs, capsaicin, and local anesthetics/antiarrythmics. Mechanistically, these drugs inhibit peripheral sensitization, modulate central sensitization, or potentiate descending inhibitory pathways. Drugs that are Food and Drug Administration-approved include carbamazepine (trigeminal neuralgia); gabapentin (PHN); pregabalin (diabetic peripheral neuropathy; fibromyalgia), duloxetine (diabetic peripheral neuropathy; fibromyalgia), and the 5% lidocaine patch (PHN). Thus, a significant portion of drug therapy used for neuropathic pain is off-label. Additional guidelines and systematic reviews on the pharmacologic management of neuropathic pain are available, including the use of opioids for neuropathic pain, as well as some of the other interventions discussed below (i.e., psychological services, rehabilitation, electrical stimulation therapies and interdisciplinary pain management programs).[112-122]

NONPHARMACOLOGIC APPROACHES

Nonpharmacologic approaches include physical modalities (physical therapy, massage, exercise, ice, and heat or ultrasound therapy), cognitive and behavioral interventions, and electrical stimulation; in some cases, more invasive neuromodulatory or neurosurgical interventions may be employed.

Rehabilitation

Rehabilitation involves the restoration of lost function. All chronic illnesses, including persistent pain, are associated with dysfunction or a loss of function. Rehabilitation is essential in order to restore function and wellness. Rehabilitation is not limited to physical rehabilitation. It includes occupational, vocational, pharmacological, social, and other forms of rehabilitation. Modalities range from passive (massage, stretching) to active (exercise, dancing). Therapy must be properly supervised and should be progressive in order to restore function with minimal distress. It is important to avoid iatrogenic trauma and exacerbation of pain.

Cognitive and Behavioral Interventions

As noted above, specific psychological traits or experiences affect an individual's response to pain and suffering. Behavioral treatments are designed to identify social and environmental factors that provoke pain behaviors or the lack of wellness behaviors. Withdrawal of attention (i.e., from spouse or caregiver) to pain behaviors is encouraged and avoidance behaviors (on the part of the patient) are discouraged through reinforcement of functional behaviors and extinguishing (ignoring) pain behaviors.[123,124] Behavioral approaches also employ self-regulatory treatments for chronic pain that teach patients to control certain bodily responses through relaxation, hypnosis, and/or biofeedback. Time-contingent instead of pain-contingent drug use may be a part of this strategy as well, although this approach does not work especially well in patients who experience

spontaneous, paroxysmal pain. Graduated activity exposure or pacing is another behavioral strategy used to help patients with persistent pain regulate and gradually increase their activity level.

Numerous psychological approaches exist to facilitate adaptation and self-management of symptoms. The most common approaches include insight-oriented therapies, behavioral treatment, and cognitive-behavior therapy (CBT). In addition, several techniques based on these models have been used, such as motivational interviewing, biofeedback, relaxation, guided imagery, hypnosis, and meditation, either independently or as part of comprehensive rehabilitation.[125]

Cognitive therapy consists primarily of education and is generally employed in conjunction with behavioral therapy. It demands patient participation and transfers the responsibility from an external to an internal locus of control, attempting to make the patient aware of the implications of pain and to better align expectations of treatment.

CBT combines the two approaches, and thus represents a selected combination and integration of treatments aimed at reducing or extinguishing the influence of the factors that reinforce or maintain patients' maladaptive behaviors, beliefs, and patterns of thought.[126] Often the first stage in CBT is to educate and provide a credible rationale for treatment by addressing the causes and consequences of pain. This can assist in understanding the perpetuation of pain, disability, and distress and in challenging erroneous beliefs, fears, and maladaptive avoidance behavior. Patients are taught to develop insights into the nature of self-defeating patterns of thinking and develop ways of challenging the premises from which these thoughts develop. This can lead to reversal of symptom-contingent declines in activity; crafting achievable goals that can be reinforced; and fostering anger management, stress reduction, and development of self-relaxation responses.

Published randomized controlled trials provide good evidence for the effectiveness of CBT or behavior therapy for certain chronic pain conditions (i.e., back pain, fibromyalgia) in adults.[127,128] However, a recent systematic review of cognitive and behavioral interventions for the management of persistent neuropathic pain in adults found little evidence for a significant effect on pain intensity.[129] Another systematic review of 40 randomized controlled trials of psychological therapy evaluated treatment effects on pain, disability, and mood. This review found that both CBT and behavioral therapy have weak effects in improving pain and minimal effects on disability but are more effective in altering mood outcomes.[130] The objective is to help patients acquire a sense of hopefulness, resourcefulness, and action to replace their more typical feelings of hopelessness, stress reactivity, and passivity.[125]

Multidisciplinary Treatment

Behavioral approaches are generally embedded in a comprehensive, multimodal pain treatment program. Patients who suffer from persistent pain experience higher rates of comorbid psychiatric disorders (e.g., depression, anxiety), as well as sleep disturbances. Effective treatment of these conditions must be part of the management plan.

Comprehensive treatments aim to eliminate maladaptive pain-related behaviors, achieve pain control, and improve coping through use of the above-noted techniques in combination with an interdisciplinary team approach to improve psychological functioning, reduce disability, and achieve rehabilitation.[131] A multimodal approach requires the combined efforts of: (1) a physician(s) knowledgeable in pharmacologic and/or interventional procedures; (2) a psychiatrist or other mental health professional to diagnose and treat psychiatric conditions that may result

from, cause, or exacerbate pain and suffering; referral for biofeedback, cognitive-behavioral techniques, group therapy, and counseling are warranted early in the course of treatment in patients with psychosocial impairment; (3) a physical therapist or rehabilitation specialist to assess physical conditioning requirements; physical therapy referral is useful for neuromuscular rehabilitation, gait and prosthetic device assessment, therapeutic exercise instruction, desensitization (especially in patients with allodynia and hyperalgesia), and electrical stimulation trials (if warranted); and (4) nurses knowledgeable about these approaches who serve to improve team function and provide valuable assistance in sustaining patient optimism and participation.

Several studies have evaluated the clinical- and cost-effectiveness of multidisciplinary pain centers, generally supporting their efficacy.[132-135] A recent systematic review of multidisciplinary treatments for persistent pain showed they were effective in patients with chronic low back pain and fibromyalgia but exhibited less robust effects in patients with persistent pain of mixed etiology.[139] A more recent investigation found that changes in depression and disability were associated concurrently with changes in pain beliefs and catastrophizing in patients undergoing multidisciplinary treatment.[136] Patients who are able to accept their condition are likely to benefit most from the treatment in terms of pain reduction, and such interventions also facilitate return to work.[137-139]

Comment. In a general sense, it must be noted that psychological and multidisciplinary interventions for patients with persistent pain have been validated mostly in patients with chronic nociceptive pain, mixed pain states (such as failed low back syndrome), and fibromyalgia. Because such conditions result in substantial reductions in health-related quality of life, and have comorbidities that increase distress and exacerbate the pain experience, it has been assumed that the efficacy of behavioral and multidisciplinary approaches noted in patients with chronic noncancer pain also extends to maldynia. However, the evidence base for this conclusion in maldynia *per se* is lacking, and further trials, enriched with such patients, are warranted.[140]

INTERVENTIONAL/INVASIVE APPROACHES TO PAIN MANAGEMENT

When systemic or topical pharmacotherapy and other noninvasive approaches provide inadequate relief in patients with maldynia, interventional approaches may be used, including reversible blockade with local anesthetics with and without steroids, intraspinal opioid delivery, spinal cord stimulation or stimulation of specific central nervous system structures, and various neuroablative procedures (e.g., dorsal rhizotomy, neurolytic nerve block, intracranial lesioning). Neuroablative procedures are not reversible and should be reserved for carefully and properly selected patients with intractable pain.

Nerve Blocks

The interruption, interference, or blockade of painful stimuli has been used in the management of pain for several decades. Acute, chronic, and postoperative pain can be diminished with various types of regional anesthesia or specific nerve blocks. In the setting of chronic pain management, various peripheral nerve blocks can be diagnostic, prognostic, or therapeutic in nature. Nerve blocks are generally most useful when a specific nerve or limb is affected. Neural blockade may help differentiate a peripheral source of pain from a neuroma or entrapped nerve root, identify sources of referred pain, or assist in distinguishing somatic from visceral pain.

Sympathetic ganglion blocks are widely employed for diagnostic and therapeutic purposes (e.g., diagnosis of sympathetically maintained pain; neuropathic pain, including phantom limb pain; complex regional pain syndrome; and ischemic pain). If analgesia is afforded with local anesthetic

blockade, chemical or thermal neurolysis may be used in an attempt to provide long-term relief. Many case reports, case series, and retrospective reviews have been published, but few prospective placebo-controlled, blinded studies exist.[141] Controlled evidence supports the use of neurolytic blocks in patients with low back pain, head, neck and shoulder pain, fibromyalgia, complex regional pain syndrome, and cancer pain. The strongest evidence exists for celiac plexus/splanchnic neurolytic blockade for cancer pain and lumbar sympathetic block or neurolysis for early treatment of reflex sympathetic dystrophy and lower extremity ischemic pain.[141,142]

Epidural Injections

Epidural steroid injections (with or without local anesthetics) may be used as part of a multimodal treatment regimen to provide pain relief in selected patients with radicular pain or radiculopathy, particularly for patients with back, leg, and neck pain.[143]

Neuromodulation

In the past 25 years, the field of pain management has increasingly incorporated technologies of neurostimulation as part of the treatment algorithm for patients with maldynia. Methodologic problems are encountered in blinding, recruitment, and assessment in nearly all published trials of these interventions. Nevertheless, patients entered in these trials have generally suffered for extended periods, and many have reported substantial relief.

Transcutaneous Electrical Stimulation (TENS) for Chronic Pain. TENS is used in a variety of clinical settings to treat a range of acute and persistent pain conditions and has become popular with patients and health care professionals of different disciplines. By applying peripheral stimuli (rubbing, vibration, heat, cold), or in the case of TENS, electrical stimulation, directly over the area of pain, sensory information from larger diameter (non-pain carrying) afferents is activated, and affects the processing of pain impulses within the dorsal horn of the spinal cord. TENS is generally believed to be a safe and relatively noninvasive intervention that can be used to alleviate many different types of pain, including neuropathic pain, primarily diabetic peripheral neuropathy.[144] However, systematic reviews have concluded there is insufficient evidence to draw any conclusions about the effectiveness of TENS for the treatment of persistent pain in adults, or in the treatment of chronic lumbar back pain.[145,146]

Spinal Cord Stimulation. Spinal cord stimulation (SCS) is a form of therapy used to treat certain types of persistent pain. An array of stimulating metal contacts is positioned in the dorsal epidural space, or sometimes in the subarachnoid space. An electrical field is generated through connection of the contacts with an electrical generator. The leads can be implanted by laminectomy or percutaneously, and the source of power is supplied by an implanted battery or by an external radio-frequency transmitter. The resulting field presumably stimulates DRG axons and dorsal column fibers.[147,148] The goal is to create a field of (tolerable) paresthesias that overlap and cover the anatomic distribution of pain reported by the patient. A temporary trial of stimulation, most commonly performed with percutaneous lead placement, is required to identify patients who might benefit.

Spinal cord stimulation has been examined in randomized trials of patients with failed back syndrome (FBSS) and complex regional pain syndrome (CRPS), and case series using SCS for neuropathic conditions other than FBSS and CRPS have been evaluated.[149] Practice guidelines on the use of spinal cord stimulation in the treatment of persistent neuropathic pain also have been developed.[148,149] Indications include failed back surgery syndrome, complex regional pain syndrome, peripheral neuropathic pain, phantom limb/postamputation syndrome, recalcitrant PHN,

root injury pain, and spinal cord injury or lesions.[148,150-152] It also is being used in the management of pain associated with multiple sclerosis, pain due to ischemic peripheral vascular disease, and interstitial cystitis.[148,149,153]

Motor Cortex/Deep Brain Stimulation

Direct stimulation of the brain, either of the motor cortex, or of deep structures, including the thalamus and perivnetricular gray, is reserved for the treatment of complex central and neuropathic pain syndromes that have proven refractory to medical treatment, including post-stroke pain, deafferentation pain, unilateral neuropathic pain, and some neuropathic pain states of peripheral origin.[142,156-157]

SUMMARY AND CONCLUSION

Neural damage to either the peripheral or central nervous system provokes maladaptive responses in nociceptive pathways that generate and amplify spontaneous pain. Multiple processes are involved, including peripheral and central sensitization, ectopic activity, neuronal cell death, disinhibition, altered gene expression, and abnormal sprouting and cellular connectivity. A series of neuro-immune interactions underlie many of these mechanisms. Imaging studies have shown that several neuropathic pain conditions are associated with functional, structural, and chemical changes in the brain.

As defined, maldynia is distinct from normal, nociceptive pain triggered by noxious stimuli. It can be triggered by persistent nociceptive stimuli or frank neural injury. A series of adaptive and, eventually, maladaptive changes occur in the function and properties of pain-carrying fibers and other sensory neurons, including phenotypic changes and alterations in gene expression, as well as the fundamental properties of specific neurons and sensory pathways. These changes involve not only neuronal pathways, but also oligodendrocytes, satellite cells in the DRG, components of the peripheral immune system, spinal microglia, and astrocytes. As such, maldynia is a multidimensional process that may warrant consideration as a chronic disease not only affecting sensory and emotional processing, but also producing an altered brain state, based on both functional imaging and macroscopic measurements. A better understanding of these pathophysiologic changes underscores the importance of adequate treatment of persistent nociceptive pain, and the need for a comprehensive approach to the management of patients with neural injury. Use of the term maldynia also has been posited as allowing patients the opportunity to better grasp the impact of changes in their nervous system and to minimize prevailing pejorative and judgmental viewpoints regarding their experience of persistent pain.

Despite recent advances in understanding of the pathology related to nervous system injury, the management of neuropathic pain and secondary maldynia remains a challenge. Patients who have substantial disability and psychosocial problems and who have not benefited from conventional pain treatments are often referred to multidisciplinary pain clinics. These multimodal programs aim to eliminate maladaptive pain-related behaviors, achieve pain control, and improve coping through biopsychosocial techniques in combination with an interdisciplinary team approach to improve psychological functioning, reduce disability, and achieve rehabilitation. These programs have largely been validated in patients with chronic noncancer pain or certain mixed pain states, but not in patients with maldynia per se. A number of interventional approaches, including nerve blocks, spinal cord stimulation, and cortical stimulation may be required when patients do not respond adequately to medical, psychological, and pharmacologic management. Although a broad array of treatments for pain patients are discussed in this report, including cognitive, behavioral,

and physical therapy approaches, such approaches require a "pain medicine specific" approach in order to be most successful.

Finally, although the concept of maldynia is appealing as an overarching view of the (maladaptive) pathophysiologic changes accompanying neural injury, many causes of neuropathic pain exist, and the preferred treatment for many of these conditions is based on the precipitating disease, injury, or syndrome. As previously noted, neuropathic pain is initiated or caused by a primary lesion or dysfunction in the nervous systems. From that point of view, the term (primary) maldynia does not currently provide any additional prognostic or treatment value over use of the term neuropathic pain. However, neuropathic pain generally does not encompass (secondary) maldynia which results from inadequately relieved persistent nociceptive stimulation. Thus, it is important that clinicians recognize the need for adequate management of persistent nociceptive pain to avoid the potential downstream neurological consequences that characterize maladaptive pain responses.

RECOMMENDATION

The Council on Science and Public Health recommends that the following statement be adopted in lieu of Resolution 525 (A-08) and the remainder of this report be filed.

> That our American Medical Association disseminate Council on Science and Public Health Report 5 (A-10), "Maldynia: Pathophysiology and Nonpharmacologic Approaches," to physicians, patients, payers, legislators, and regulators to increase their understanding of issues surrounding the diagnosis and management of maldynia (neuropathic pain). (Directive to Take Action)

Fiscal Note: $1,000

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Table 1. Common Types of Neuropathic Pain

Peripheral

- Acute and chronic inflammatory demyelinating polyradiculopathy
- Alcoholic
- Chemotherapy-induced
- Complex regional pain syndrome
- Entrapment neuropathies (eg, carpal tunnel syndrome)
- HIV sensory neuropathy
- Post-surgical (ie, postmastectomy pain or post-thoracotomy pain)
- Idiopathic sensory
- Nerve compression, including tumor infiltration
- Nutrition deficiency-related
- Diabetic
- Phantom limb pain
- Postherpetic neuralgia
- Postradiation plexopathy
- Radiculopathy (cervical, thoracic, lumbar)
- Toxin-related
- Trigeminal neuralgia)
- Post-traumatic

Central Neuropathic Pain

- Compressive myelopathy
- HIV myelopathy
- Multiple sclerosis-related
- Parkinson’s disease-related
- Postischemic myelopathy
- Postradiation myelopathy
- Poststroke pain
- Post-traumatic spinal cord injury
- Syringomyelia

Table 2. Definition and assessment of negative and positive sensory symptoms or signs in neuropathic pain

Symptom/sign	Definition	Assessment
Negative		
Hypoesthesia	Reduced sensation to non-painful stimuli	Touch skin with painter's brush, cotton swab or gauze
Pallhypoesthesia	Reduced sensation to vibration	Apply tuning fork to bone or joint
Hypoalgesia	Reduced sensation to painful stimuli	Prick skin with single pin stimulus
Thermohypoesthesia	Reduced sensation to cold or warm stimuli	Touch skin with objects of 10°C (metal roller, glass of water, coolants like acetone) Touch skin with objects of 45°C (metal roller, glass of water)
Spontaneous		
Paraesthesia	Non-painful ongoing sensation (ant crawling)	Grade intensity (0-10); Area in cm^2
Paroxysmal pain	Shooting electrical attacks for seconds	Number per episode; Grade intensity (0-10) Threshold for evocation
Superficial pain	Painful ongoing sensation, often of burning quality	Grade intensity (0-10); Area in cm^2
Evoked		
Mechanical dynamic allodynia	Normally non-painful light-pressure moving stimuli on skin evoke pain	Stroking skin with painter's brush, cotton swab or gauze
Mechanical static allodynia	Normally non-painful gentle static pressure stimuli on skin evoke pain	Manual gentle mechanical pressure to the skin
Mechanical punctate or pinprick hyperalgesia	Normally stinging-but-not-painful stimuli evoke pain	Manual pricking of the skin with a safety pin, sharp stick or stiff von Frey hair
Temporal summation	Repetitive application of identical single noxious stimuli is perceived as increasing pain sensation (wind-up-like pain)	Pricking the skin with safety pin at <3s intervals for 30s
Cold allodynia	Normally non-painful cold stimuli evoke pain	Touch skin with objects of 20°C (metal roller, glass of water, coolants like acetone) Control: touch skin with objects of skin temperature
Heat allodynia	Normally non-painful heat stimuli evoke pain	Touch skin with objects of 40°C (metal roller, glass of water) Control: touch skin with objects of skin temperature
Mechanical deep somatic allodynia	Normally non-painful pressure on deep somatic tissues evokes pain	Manual light pressure at joints or muscle

Table 3. Prevalence of symptoms across causes of neuropathic pain

	PHN	DPNP	PPN	Nerve Trauma	Radiculo-pathy	Trigeminal Neuralgia	Spinal Trauma	MS	Syrinx	Stroke
Burning Pain	89.8	62.8	58.5	51.1	65.1	16.7	76	56.2	75	74.2
Deep Pain	28.5	68.6	62.3	58	51.2	22.2	74	62.5	60	64.5
Evoked Pain	91.9	51.5	64.1	76	44.2	61.1	70	75	62.5	74
Parasthesia/ Dysthesia	30	82.9	84.9	86	81.4	33	80	84.4	87.5	83.9
Paroxysmal pain	63.2	62.8	62.3	66.3	72	89.9	72	65.6	65	58

All values are expressed as %; **PHN**, postherpetic neuralgia; **DPNP**, diabetic peripheral neuropathic pain; **PPN**, painful polyneuropathy (nondiabetic); **MS**, multiple sclerosis

Appendix. Glossary

Term	Definition
Allodynia	Pain due to nonnoxious stimuli (clothing, light touch) when applied to the affected area. May be mechanical (eg, caused by light pressure), dynamic (caused by nonpainful movement of a stimulus), or thermal (caused by nonpainful warm, or cool stimulus)
Analgesia	Absence of pain in response to stimulation that would normally be painful.
Anesthesia	Loss of normal sensation to the affected region
Dysesthesia	Spontaneous or evoked unpleasant abnormal sensations
Eudynia	Symptom based pain provoked by an identifiable injury or noxious stimulus
Hyperalgesia	Exaggerated response to a mildly noxious stimulus applied to the affected region
Hyperpathia	Delayed and explosive response to a noxious stimulus applied to the affected region
Hypoesthesia	Reduction of normal sensation to the affected region
Maldynia	Maladaptive pain that persists in the absence of ongoing tissue damage or injury
Neuralgia	Pain in the distribution of a nerve or nerves
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system.
Neuropathy	A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.
Nociceptor	A receptor preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged.
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
Paresthesias	Nonpainful spontaneous abnormal sensations
Phantom pain	Pain from a specific site that no longer exists (eg, amputated limb) or where there is no current injury
Referred pain	Occurs in a region remote from the source