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REVIEW ARTICLE

Maldynia: Pathophysiology and Management of Neuropathic and Maladaptive Pain—A Report of the AMA Council on Science and Public Health

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Abstract

Background. Because of disparate taxonomic arrays for classification, the American Academy of Pain Medicine has proposed categorizing pain on a neurobiologic basis as *eudynia* (nociceptive pain), Greek for "good pain," or *maldynia* (maladaptive pain), Greek for "bad pain." The latter has been viewed as maladaptive because it may occur in the absence of ongoing noxious stimuli and does not promote healing and repair.

Objective. To address recent findings on the pathogenesis of pain following neural injury and consider whether the development of maladaptive pain justifies its classification as a disease and to briefly discuss the scope of pharmacologic and nonpharmacologic approaches employed in patients with such pain.

Methods. English language reports on studies using human subjects were selected from a PubMed search of the literature from 1995 to August 2010 and from the Cochrane Library. Further information was obtained from Internet sites of medical specialty and other societies devoted to pain management.

Results. Neural damage to either the peripheral or central nervous system provokes multiple processes 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 such damage is characterized by functional, structural, and chemical changes in the brain. Such pain is maladaptive in the sense that it occurs in the absence of ongoing noxious stimuli and does not promote healing and repair.

Conclusion. As defined, 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. However, the absolute clinical value of this definition is not established.

Key Words. Maldynia; Neuropathic Pain; Maladaptive Pain

Introduction

This article addresses recent findings on the pathogenesis of neuropathic and maladaptive pain (maldynia) and

whether current understanding justifies classification of maldynia as a disease. Additionally, the scope of pharmacologic and non-pharmacologic approaches employed in patients with neuropathic pain is briefly reviewed. 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 article 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 August 2010 using the search terms "maldynia," "neuralgia," or "neuropath*," in combination with "pain," "physiopathology," "diagnosis," "management," "immune system," "imaging," "genetics," "treatment," and "cognitive therapy." 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." Articles were selected for their ability to supply information about the pathogenesis of pain and modes of therapy. 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 retrieved references. Further information was obtained from the Internet sites of the American Pain Society (http://www.ampainsoc.org), American Academy of Pain Medicine (AAPM) (http://www.painmed.org), International Association for the Study of Pain (IASP, http://www.iasp-pain.org), American Academy of Pain Management (http://www.aapainmanage.org), and the American College of Occupational and Environmental Medicine (http://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 [1]. 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 based on its location (focal, multi-focal, generalized, and referred), in a temporal fashion (acute, intermittent, or continuous), based on its site (headache, neck or back pain) and etiology (cancer or noncancer, visceral, neurogenic), and 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 word for "good pain" or *maldynia* (maladaptive pain) from the Greek word 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 can be considered maladaptive because it occurs in the absence of ongoing noxious stimuli and does not promote healing and repair. Additionally, such pain responds poorly to conventional pain medications such as opioid analgesics, acetaminophen, and nonsteroidal anti-inflammatory drugs. Accordingly, the AAPM and other proponents in the pain medicine community have advanced the notion that under such conditions, "pain becomes the disease process itself" [2–5].

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 (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 article, its use corresponds to this definition; otherwise, the 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 [FBSS]).

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) and the spinal sensory nucleus of cranial nerve V. These neurons have a unique morphology (pseudounipolar), extending one axonal process to

peripheral targets for detecting noxious stimuli and another into the spinal cord to transfer information to the central nervous system. Acute nociceptive pain is normally evoked only by stimuli that are sufficiently intense to exceed the threshold for activation of primary afferent Aδ (lightly myelinated) and C (unmyelinated) fiber nociceptors.

Nociceptors are composed of numerous varieties, either responding to a specific noxious stimulus or more commonly, exhibiting polymodal responses to chemical, thermal, severe pressure, and/or mechanical stimuli [6,7]. 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 [6,7]. Under certain conditions, impulses can travel antidromically to the peripheral primary afferent terminal, resulting in the local release of various vasoactive and inflammatory mediators that can trigger local vasodilation, vascular leakage, localized edema, and infiltration of leukocytes and other immnuno-competent cells (neurogenic inflammation).

The central processes of Aδ and C-fibers terminate in a highly organized, topographic pattern in the dorsal horn of the spinal cord. The outermost thin marginal layer (Lamina I) is composed of small neurons with small receptive fields that respond primarily, and in some cases, exclusively, to noxious stimuli. Ascending projections from Lamina I mediate the affective-motivational, and to a certain extent, sensory-discriminative, aspects of human pain. Lamina II (also known as the *substantia gelatinosa*) principally contains small interneurons that modulate cells of Lamina I and V but also contains the terminals of some C-fibers. Lamina V receives convergent input from innocuous, low-threshold sensory fibers (Aβ) mediating touch and tactile stimuli and high-threshold noxious Aδ fibers, and C fibers; the latter have a large receptive field and respond to a broad range of stimulus intensities composed of so-called wide dynamic range (WDR neurons). Central projections from Lamina V mediate somatic responses and sensory decoding and also may play a role in referred pain [8]. Primary afferent terminals in the dorsal horn are subject to several local inhibitory influences, including voltage-gated Ca^{2+} channels, and inhibitory gamma amino butyric acid (GABA), opioid, and cannabinoid receptors. Local inputs receiving noxious stimuli also are subject to descending inhibitory pathways from higher centers that relay through the brainstem as well as to certain facilitatory pathways.

Dorsal horn neurons ascend to form the spinothalamic tract and spinoreticular pathways that relay noxious information to the thalamus and higher cortical centers [9]. Ascending pain signals from dorsal horn cells are mediated to a large extent by rapidly conducting fibers that release 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 composed of 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 [10–12]. Thus, modulation of the primary nociceptive stimulus occurs at local and segmental levels of the spinal cord in response to descending pathways and at higher subcortical and cortical levels, affecting the discriminative, emotional, and cognitive aspects of pain [9,13,14].

Inflammatory Pain

With tissue injury sufficient to provoke an inflammatory response, substances that are released from damaged cells as well as various inflammatory mediators can directly activate nociceptors, triggering both peripheral sensitization of nociceptors and central sensitization of dorsal horn neurons, leading to both spontaneous pain and hyperalgesia (see later section). The sensitization process involves changes in neuronal ion channels, responsiveness, and function and is invariably associated with persistent pain states. With peripheral and central sensitization, low threshold stimuli that are normally innocuous trigger pain and the pain associated with noxious stimuli is augmented and prolonged. Heightened pain sensitivity also may develop in adjacent uninjured areas [15,16]. Similar to (typical) nociceptive pain, inflammatory pain disappears after healing of the initial tissue injury and resolution of inflammation; however, in chronic inflammatory disorders such as rheumatoid arthritis, the pain persists as long as inflammation and noxious stimuli are evident [17].

Neuropathic Pain

Neuropathic pain is defined by the International Association for the Study of Pain [1] 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 [18]. Peripheral neuropathic pain results from lesions to the peripheral nervous system caused by mechanical trauma, metabolic diseases, neurotoxic chemicals, infection, or tumor invasion [19]. Central neuropathic pain most commonly results from spinal cord injury, stroke, or multiple sclerosis [20]. 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 suffer from secondary maldynia.

Table 1 Common Types of Neuropathic Pain [Adapted from Baron [32]]

Peripheral
Acute and chronic inflammatory demyelinating polyradiculopathy
Alcoholic
Amyloid
Chemotherapy-induced
Complex regional pain syndrome
Diabetic neuropathy
Entrapment neuropathies (e.g., carpal tunnel syndrome)
HIV sensory neuropathy
Hypothyroidism
Hereditary sensory neuropathies
Ischemic neuropathy
Nerve compression, including tumor infiltration
Nutrition deficiency-related
Phantom limb/stump pain
Polyarteritis nodosa
Postherpetic neuralgia
Post-surgical (i.e., postmastectomy pain or post-thoracotomy pain)
Post-traumatic neuralgias
Postradiation plexopathy
Radiculopathy (cervical, thoracic, lumbar)
Toxin-related
Trigeminal neuralgia
Central Neuropathic Pain
Compressive myelopathy
HIV myelopathy
Multiple sclerosis-related
Parkinson's disease-related
Postischemic myelopathy
Postradiation myelopathy
Poststroke or infarction (thalamus/spinal cord) pain
Post-traumatic spinal cord injury
Syringomyelia

Processes Common to Inflammatory and Neuropathic Pain

Inflammatory and neuropathic pain shares some common features, namely peripheral and central sensitization and neuro-immune interactions. The following organizational scheme and framework for the discussion on the pathophysiology of maladaptive pain is based on a view previously articulated by Costigan et al. [4].

Peripheral Sensitization and Primary Hyperalgesia

With tissue injury and inflammation, nociceptors are exposed to various substances from damaged cells as well as substances released or generated as part of the inflammatory response. These include purine nucleotides, neurotransmitters, kinins and other peptides, cytokines/chemokines, arachidonic acid metabolites, neurotrophic factors, and excess protons due to the more acidic nature of the inflammatory environment. These signaling molecules can either directly activate or sensitize nociceptors [6–8]. Sensitization is achieved in part by an increased expression of ion channels involved in nociceptor signaling [4]. Peripheral nerve damage causes an overpopulation of specific Na_V and TRPV1 channels [26] in the primary afferent terminal, axonal sprouts in the region of injury, demyelinated areas, and some adjacent uninjured nociceptors at the lesion site. Some of these channels appear to be necessary for the expression of neuropathic pain following neural injury [27–29]. Furthermore, point mutations affecting the function of certain Na_V channels cause painful inherited neuropathies (i.e., primary erythromelalgia and paroxysmal extreme pain disorder) [30,31].

Peripheral sensitization reduces 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 traffic in a retrograde direction, thereby affecting DRG and dorsal horn cells.

Central Sensitization, Secondary Hyperalgesia, and Mechanical Allodynia

As a consequence of injury-induced increases in peripheral nociceptor activity, secondary neuropastic changes are triggered in their spinal cord targets that ultimately enhance the function of these neurons and other components in nociceptive pathways. These changes include increased membrane excitability, promotion of synaptic transmission, and reduced local inhibition. 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" [32]. Together, these changes constitute the phenomenon of central sensitization. In addition, normally innocuous tactile stimuli become capable of generating pain responses via low-threshold Aβ mechanorecptors.

From a mechanistic viewpoint, enhanced co-release of glutamate and peptide neurotransmitters (e.g., substance P, calcitonin gene-related peptide) from nociceptors activates NMDA receptors, which increases the intracellular calcium load in dorsal horn neurons. As previously noted, nerve injury increases the spinal cord expression and/or activity of voltage- and ligand-gated ion channels and attendant receptors; these changes and the elaboration of neuro-immune factors (see later section) that directly stimulate DRG cells promote dorsal horn neuron hyperexcitability. Nerve injury also modifies gene expression in nociceptive-specific Lamina I neurons, provoking a change in their functional characteristics resembling those of WDR (as in Lamina V). Accordingly, when these neurons are now subjected to repeated stimulation, they respond

with an exaggerated response (wind-up) [33]. The latter contributes but is not sufficient to account for central sensitization [33].

Central sensitization contributes to persistent pain states whether they are inflammatory, neuropathic, and dysfunctional in nature [4]. Dysfunctional pain has been described by Costigan et al. [4] as certain persistent pain conditions (e.g., fibromyalgia, interstitial cystitis, irritable bowel syndrome) in which there is "no identifiable noxious stimulus nor any detectable inflammation or damage to the nervous system." Clinically, central sensitization manifests as pain sensitivity beyond the site of tissue damage or inflammation (secondary hyperalgesia). Corresponding synaptic changes may occur in more central components of the pain matrix, which may contribute to the affective, cognitive, and other learned behaviors typically encountered in patients with persistent pain [34,35].

Neuro-Immune Interactions

Reciprocal interactions among immune surveillance cells, glial cells, and neurons are responsible for triggering and maintaining some of the key pathophysiologic changes and characteristics of inflammatory neuropathic pain [36]. Glial and immune cells play a role in amplifying peripheral nociceptor responses and pain during inflammation and also contribute to peripheral and central processes that come into play after neural injury (see later section).

Psychological Issues in Patients with Persistent Pain

Psychological issues or variables are exceedingly important when managing patients with chronic ailments, especially in the presence of persistent pain. A number of studies have evaluated the influence of psychosocial and psychological factors on pain severity, functioning, disability, and other outcomes in such patients.

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 [37,38]. Concordantly, the presence of persistent pain markedly increases the occurrence of depression; anywhere from one-third to more than one-half of such patients referred to pain clinics have major depression [39]. Regardless of whether they are causes or effects, comorbid psychiatric conditions complicate patient management [40]. Depression in patients with chronic pain is associated with [41] "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" [42–44]. 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 [45]. Pain-related cognitions and emotional decision-making abilities contribute to the variance in how patients describe their pain intensity, and anxiety and avoidance beliefs are related to poorer function in patients with chronic pain [46].

The extent of pain catastrophizing shapes the experience of acute and persistent pain and predicts pain-related outcomes [47]. Pain-related catastrophizing is broadly conceived as a "set of exaggerated and negative cognitive and emotional schema that emanate during actual or anticipated pain" [48]. 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" [47]. 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 [48].

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 [49]. These psychological factors must be addressed in managing patients afflicted with persistent pain [50].

Pathophysiology of Maldynia—Mechanisms of Neuropathic and Maladaptive 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). Knowledge also has been gained from some human models and the results of human imaging and genetic studies. 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 [36]. Some of these processes assist in healing and normative repair [51,52] (i.e., clearing cellular debris, synaptic remodeling, remyelination), but many are maladaptive and tend to perpetuate pain symptoms such as sensitization, ectopic impulse generation, apoptosis, phenotypic switching, and rewiring of neuronal circuits [53].

Ectopic Impulse Generation

Peripheral sensitization can trigger spontaneous depolarization (ectopic activity) in primary afferents, which, in turn, activate and sensitize their central targets. 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 [2]. Sympathetic sensory coupling is thought to contribute to inflammatory pain, the pain associated with complex

regional pain syndrome (CRPS), diabetic neuropathy, postherpetic neuralgia, phantom limb sensations, and other conditions [8,54–56]. As previously noted, ectopic discharges originating in the cell body of injured primary afferents can cause antidromic stimulation, the release of mediators, and (neurogenic) inflammation at the periphery.

A loss of normal afferent input due to neural injury (deafferentation) also can lead to sensitization and ectopic discharges in spinal cord or thalamic neurons [20]. After spinal cord injury, neuroimmune processes triggered by axonal degeneration can trigger ectopic activity in neighboring intact neurons that then behave as central pain generators.

Low-Threshold Aβ Fiber-Mediated Pain

In addition to their normal sensory role of mediating touch, pressure, vibratory, and joint movement sensations, low-threshold Aβ fibers mediate the suppression of nociceptive pain caused by rubbing the affected area (the "gate" control theory). However, when nerve injury creates conditions of disinhibition (see later section), Aβ 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 primary afferent or Aβ fibers to "sprout" into the more superficial layers of the spinal cord (Lamina II). Regenerative sprouts may exhibit ectopic activity or be activated by relatively weak stimuli [57]. Combined with central sensitization, these adaptations manifest clinically as the ability of stimuli from large myelinated, low-threshold Aβ receptors to generate sensations of pain or tenderness (dynamic mechanical allodynia) [57–60].

Disinhibition

Local inhibition in the dorsal horn is integral to the normal process of filtering, integrating, and coding sensory signals. Local inhibitory circuits and interneurons use a variety of neurotransmitters (e.g., opioids, cannabinnoids, GABA, neuropeptide Y, adenosine). These local influences and descending inhibitory pathways (e.g., norepinephrine, opioids) serve to dampen the influence of noxious stimuli. Activation of these systems opposes the onset of enhanced pain responses (hyperalgesia and/or allodynia) after neural injury. However, following peripheral nerve injury, primary sensory and dorsal horn neurons [61] as well as spinal cord inhibitory neurons (especially those containing GABA) degenerate [4,61]. The loss of inhibitory tone (disinhibition) creates conditions where pain transmission is facilitated.

Neuro-Immune Contributions

Collectively, glial cells are far more prevalent than neurons in the central nervous system. Subtypes include resident and perivascular microglia, astrocytes, and oligodendrocytes; the latter provides the sheath for central myelinated neurons and are therefore important in the repair of damaged neurons. It is now widely recognized that microglia, and to a lesser extent, astrocytes, play important roles in inducing and maintaining neuropathic pain states.

Microglia (and macrophages) are recruited and activated in the vicinity of the central terminals of injured sensory nerves [36]. Activated microglia produce numerous neuromodulators and inflammatory mediators (Il-1B, IL-6, TNFα, PGE_2, nitric oxide, and brain derived neurotrophic factor [BDNF]) that activate neurons [36]. However, microglia also express their own receptors for various substances including purines (adenosine triphosphate [ATP]), neuropeptides, neurotransmitters, chemokines, and neurotrophic factors that can modulate glial cell activity. Accordingly, glia have the capacity to actively communicate in a reciprocal fashion with neurons.

Important glial signaling pathways involve purine nucleotides (ATP), chemokines, and toll-like receptors (TLRs), a family of 12 evolutionarily conserved membrane proteins that provide surveillance for immunologic threats [62]. ATP-stimulated glia increase nociceptor sensitivity, activate pain carrying neurons in the dorsal horn, and induce mechanical allodynia. 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 exposure to ATP-activated microglia induces mechanical allodynia [63–65].

Astrocytes also are in a position to influence neuronal activity as they encapsulate nerve endings, are in close proximity to nerve cells, and influence the extracellular fluid milieu. Similar to microglia, astrocytes express various functional receptors for neurotransmitters (glutamate, purines, substance P) and pattern recognition receptors such as TLRs. Activated astrocytes express various so-called mitogen-activated protein kinases (MAPK) [66,67]. MAPKs are a small family of enzymes that play an important role in intracellular signal transduction and gene expression via different signaling cascades.

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. The term "cytokine" is commonly used to refer to substances with immunomodulating effects such as interleukins and interferons. Chemotactic cytokines (chemokines) represent a family of more than 50 small, secreted proteins (70 to 100 amino acids in length) that mediate white blood cell migration and accumulation at sites of inflammation. Chemokines and chemokine receptors also are widely expressed in the nervous system where in addition to controlling leukocyte infiltration, they subserve more rudimentary processes involving stem cell migration, axonal path finding, and the architecture of neurotransmission.

Neurons and glia both release and respond to chemokines [36,68,69]. TLRs upregulate the products of interfer-

ons and the expression of proinflammatory cytokines [62]. Experimentally induced neuropathic pain is substantially reduced when purinergic receptors are blocked or certain chemokine receptors or TLRs are knocked out [65,70,71].

Immune Surveillance and Response Following Neural Injury

In the peripheral nervous system, macrophages both clear cellular debris and serve as antigen-presenting cells to activate T-lymphoctyes. Both macrophages and T-cells communicate via cytokines and chemokines with neurons, oligodendrocytes, Schwann cells, and spinal microglia. Macrophages and microglia participate in the degeneration following axonal injury. Following peripheral nerve injury, resident spinal microglia in close proximity to the injured afferent express chemokine receptors and are strongly activated in the dorsal horn, close to the central terminals of injured afferents [72].

As noted earlier, microglial cells release mediators capable of activating signaling cascades that induce and maintain maladaptive pain states [73,74]. Mediators released by microglia and astrocytes, and the chemokines/cytokines elaborated by dorsal root ganglion cells directly activate nociceptors, increasing the excitability of nociceptive sensory neurons (peripheral sensitization) and stimulating neighboring chemokine-expressing neurons [75,76]. Action potentials are elicited in part by alterations in the expression and function of the transient receptor potential channels (TRPV1; TRPA1) and increases in sodium and calcium currents [68]. A similar response triggered by peripheral immune cells and microglia in the spinal cord activates dorsal horn nociceptive neurons (central sensitization).

Direct administration of chemokines elicits allodynia in animal models [71]. 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 [36,77].

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, contributing to the development and persistence of pain after nerve injury.

Genetic Determinants of Pain

A substantial minority of individuals who experience neural injury do not develop neuropathic pain. Therefore, 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 [78]. As a baseline, twin studies reveal that genetic factors contribute 20–60% of the variance in nociceptive pain sensitivity [79,80]. Some rare recessive conditions affecting sodium channels are associated with either pain insensitivity or extreme pain [78]. In addition, Fabry disease, a rare X-linked recessive lysosomal storage disease, may be characterized by burning neuropathic pain. Based on gene association studies, some candidate genes related to pain sensitivity are polymorphic variants of the catechol-O-methyltransferase, *mu* opioid receptor, melanocortin-1 receptor, and the TRPA1 genes; certain haplotypes of the enzymes involved with tetrahydrobiopterin synthesis also are related to pain sensitivity [81–84].

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 [85]. Activation in these areas is related to sensory-discriminative aspects of pain, affective-emotional aspects, and cognitive aspects of pain.

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, CRPS, phantom pain, chronic migraine, irritable bowel syndrome, fibromyalgia, and trigeminal neuralgia compared with age-matched control subjects [86–94]. The magnitude of such changes tends to correspond with the duration of symptoms. However, patients with persistent pain frequently have comorbid conditions, including anxiety and mood disorders, a more sedentary lifestyle, and lengthy medication history, factors that could be related to these structural findings [90].

PET studies have shown decreases in brain opioid receptor binding in patients with central neuropathic pain [95]. SPECT studies have demonstrated reduced thalamic activity in patients with chronic pain [96]. 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) [97]. fMRI has been used to study the discriminative sensory, emotional, motivational, and modulatory responses in particular regions of the brain and brain stem. Based on fMRI studies in patients with peripheral nerve lesions, brain areas beyond the normal “pain matrix” are activated during allodynic stimulation [98]. In one study of subjects who had previously experienced allodynia, just imagining that touch is

Table 2 Definition and assessment of negative and positive sensory symptoms or signs in neuropathic pain. Adapted from Baron [32]

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 on skin 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	Pricking the skin with safety pin at <3 seconds intervals for 30 seconds
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

painful leads to activation of the anterior cingulate gyrus and prefrontal cortex [99]. 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 [100–102]. These findings demonstrate that neuropathic pain, similar to other major neurological and psychiatric diseases, has widespread effects on overall brain function.

Diagnosis and Management of Maldynia

Neuropathic pain typically exhibits a heterogeneous presentation including burning, tingling, paresthesias, shock-like pain, hypoesthesia, and phantom limb pain. A combination of distinct sensory symptoms typically coexist in various combinations with motor and autonomic signs; both positive and negative sensory symptoms may be manifest (see Table 2) [19,103]. Positive sensory symptoms include pain, *paresthesia* (abnormal sensation, either evoked or spontaneous), *dysesthesia* (evoked or spontaneous unpleasant, abnormal sensation), *hyperalgesia* (increased response to a normally painful stimulus), and *allodynia* (painful response to a non-noxious stimulus). Negative sensory symptoms involve a loss of sensitivity to stimulation in general and painful stimuli in particular (*hypoesthesia* and *hypoalgesia*).

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 [4]. 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 [79,104]. These dysfunctional pain syndromes share some features with neuropathic pain, namely reduced pain thresholds (sensitization) and the presence of diffuse pain [104].

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, MRI, and electrophysiologic studies [103]. 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 [105,106]. More detailed information on the assessment of pain, quantitative sensory testing, and measures of neuropathic pain is available [107–111]. Examples of standardized scales used for rating pain intensity and for pain assessment include the Short Form McGill Pain Questionnaire [112], 100 mm visual analog scales, numeric rating and faces scales, the Neuropathic Pain Scale [113], and the Neuropathic Pain Questionnaire [114]. A 30% reduction in pain scores using such scales is deemed clinically important [115].

Management

Patients suffering from persistent, maladaptive pain generally require a comprehensive treatment strategy incorporating interdisciplinary management. Refractory pain leads to mood and anxiety disorders as well as diminished social functioning, productivity, and quality of life. A combination of pharmacologic, nonpharmacologic, psychologic, and interventional approaches are often required.

Pharmacologic Treatment of Neuropathic Pain

In a previous 2006 report, the Council systematically reviewed the pharmacotherapy of neuropathic pain [116]. In addition to opioids, tramadol, and cannabinoids, many drugs used in patients with primary maldynia are not classified as analgesics *per se*, including antidepressants, antiepileptic drugs (AEDs), capsaicin, and local anesthetics/antiarrhythmics. 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 (PHN; diabetic peripheral neuropathy; fibromyalgia), duloxetine (diabetic peripheral neuropathy; fibromyalgia), capsaicin (PHN), and the 5% lidocaine patch (PHN). Thus, a significant portion of drug therapy used for neuropathic pain is off-label. Global knowledge regarding pharmacotherapy has been limited somewhat by the fact that most clinical trials have been performed in patients with PHN or painful diabetic neuropathy. Furthermore, few direct comparisons have been made, and more data are needed on combination approaches that may improve the clinical response.

Several guidelines and systematic reviews on the pharmacologic management of neuropathic pain with drug selection and dosing guidance have been developed in the last 3 to 4 years [117–128], including those developed by the Neuropathic Pain Special Interest Group of the IASP [122], the European Federation of Neurological Societies [117] and the Canadian Pain Society [123]. First-line medications recommended by these guidelines for neuropathic pain include the following:

- Tricyclic antidepressants (e.g., nortriptyline, desipramine) or a selective serotonin/norepineprhine uptake inhibitor (e.g., duloxetine, venlafaxine). These drugs have variable inhibitory effects on the neuronal uptake of nonepinephrine (NE) and 5-HT, both of which are important components of descending control pathways originating in the midbrain that serve to diminish pain transmission at the spinal level.
- Drugs that modulate the activity of $\alpha_2\delta$ calcium channel subunits on synaptic terminals, which are activated/upregulated during central sensitization (e.g., gabapentin, pregabalin).
- Topical lidocaine for patients with localized peripheral neuropathy.
- Opioid analgesics or tramadol alone or in combination with one of the aforementioned in patients with acute or cancer-related neuropathic pain.

Carbamazepine and oxbarbazeopine are the drugs of choice for trigeminal neuralgia [129].

Topical creams with capsaicin are used to treat pain from PHN and PDN. This compound stimulates C-fiber nerve endings by binding to vanilloid-type receptors. With repeated administration, the central terminal becomes depleted of substance P, and peripheral receptive sites may degenerate, resulting in decreased pain sensations. A recent systematic review and pooled analysis confirmed that capsaicin is significantly better than placebo for the treatment of neuropathic pain [120].

Alternate or adjunctive medications include AEDs and oral or systemic local anesthetic such as lidocaine and its oral analogs. AEDs currently used for neuropathic pain are gabapentin, carbamazepine, clonazepam, lamotrigine, oxcarbazepine, phenytoin, topiramate, and valproate. Mechanisms vary among these agents, including sodium channel modulation, enhanced GABAergic function, and inhibition of Ca^{++} currents [122,129].

Many other drugs have been evaluated for their efficacy against neuropathic pain, including other antidepressants (e.g., bupropion, clomipramine, imipramine), cannabinoids, NMDA receptor antagonists (e.g., dextromethorphan, ketamine, memantine, riluzone), baclofen, other

AEDs (e.g., tiagabine, zonisamide, leviracetam), and magnesium sulfate [116,118]. Investigational compounds target the putative pathophysiologic cascade involved in the development of neuropathic pain states, including compounds that target vanilloid receptors, and antagonists for bradykinin, glycine, tumor necrosis factor, and interleukin receptors. More recently, interest has been shown in more fully evaluating the effects of botulinum toxin, higher concentration capsaicin patches, and a new AED (lacosamide) on neuropathic pain [129].

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. It includes physical rehabilitation as well as occupational, vocational, social, and other forms of rehabilitation. Modalities include both passive (massage, stretching) and active (exercise, dancing) approaches. A progressive approach is helpful in restoring function while minimizing exacerbation of pain.

Cognitive and Behavioral Interventions

Because psychological traits or experiences affect an individual's response to pain and suffering, specific approaches are needed to mitigate these influences. Behavioral treatments identify social and environmental factors that exacerbate pain behaviors or impede wellness behaviors. Avoidance behaviors (on the part of the patient) are discouraged by reinforcing behaviors that improve function and by encouraging spouses or caregivers to avoid giving attention to pain behaviors [130,131]. Adjunctive approaches such as the use of relaxation, hypnosis, and/or biofeedback can assist in teaching patients to control certain responses in an attempt to foster self-regulatory treatments for chronic pain. With pharmacologic management, time-contingent treatment instead of pain-provoked dosing can be adopted, although patients who experience spontaneous, paroxysmal pain are generally not suitable candidates for this approach. Stepwise activity exposure also is used to help patients with persistent pain to gradually increase their activity level and promote function.

Numerous psychological approaches exist to facilitate adaptation and self-management of symptoms. In patients with chronic pain, these treatments are complementary to medical management and are intended to address emotional distress and maladaptive behaviors [40]. The most common approaches include insight-oriented therapies, behavioral treatment, and cognitive behavior therapy (CBT). Several additional techniques such as motivational interviewing, biofeedback, relaxation, guided imagery, hypnosis, and meditation are used either independently or as part of comprehensive rehabilitation [132].

Cognitive therapy is composed primarily of education and is generally employed in conjunction with behavioral therapy. Patient participation is integral to the success of this approach that attempts to increase patients' awareness of the implications of their pain and to promote realistic expectations for treatment.

CBT represents a selected combination and integration of cognitive and behavioral treatments aimed at reducing the influence of factors that reinforce or maintain patients' maladaptive avoidance behaviors, assisting patients in addressing beliefs and self-defeating patterns of thought about pain that interfere with functioning, and promoting assertiveness as well as learning strategies and coping skills to better manage pain, set goals, and improve stress management [133]. By enhancing self-efficacy and the patients' internal sense of control for managing their pain, pain-related distress is diminished, physical functioning is improved, and pain-related disability may be reduced.

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 [134,135]. 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 [136]. 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 [137].

Multidisciplinary Treatment

Behavioral approaches are generally embedded in a comprehensive, multimodal pain treatment program. Patients who suffer from persistent pain have higher rates of comorbid psychiatric disorders (e.g., depression, anxiety) and 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 aforementioned techniques in combination with an interdisciplinary team approach to improve psychological functioning, reduce disability, and achieve rehabilitation [138]. A multimodal approach requires the combined efforts of the following: a physician(s) knowledgeable in general medicine and pharmacologic and/or interventional procedures for pain management; a psychiatrist or other mental health

professional to diagnose and treat dysfunctional pain disorders, comorbid psychopathology that may result from, cause, or exacerbate pain and suffering, and cognitive distortions; a physical therapist or rehabilitation specialist to assess physical conditioning requirements and to teach pain control modalities; and nurses knowledgeable about these approaches who serve to improve team function and provide valuable assistance in sustaining patient optimism, the development of coping strategies, and overall healthy behaviors.

Referral for biofeedback, cognitive–behavioral techniques, group therapy, and counseling are warranted early in the course of treatment in patients with psychosocial impairment. Physical therapy referral is useful for musculoskeletal rehabilitation and therapeutic exercise instruction.

Several studies have evaluated the clinical effectiveness and cost-effectiveness of multidisciplinary pain centers, generally supporting their efficacy [139–143]. 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 [143]. 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 [144]. 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 [145,146].

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 [147].

Interventional 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 (SCS) 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; CRPS; 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 [148]. Controlled evidence supports the use of neurolytic blocks in patients with low back pain, head, neck and shoulder pain, fibromyalgia, CRPS, 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 [148,149].

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 [149].

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. Methodological 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 [150]. 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 [151,152].

SCS

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 [153,154]. 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.

SCS has been examined in randomized trials of patients with FBSS and CRPS, and case series using SCS for neuropathic conditions other than FBSS and CRPS have been evaluated [155]. Practice guidelines on the use of SCS in the treatment of persistent neuropathic pain also have been developed [154,155]. Indications include failed back surgery syndrome, CRPS, peripheral neuropathic pain, phantom limb/postamputation syndrome, recalcitrant PHN, root injury pain, and spinal cord injury or lesions [154,156–158]. It also is being used in the management of pain associated with multiple sclerosis, pain due to ischemic peripheral vascular disease, and interstitial cystitis [154,155,159].

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 [149,160–163].

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 neuroimmune 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, SCS, and cortical stimulation may be required when patients do not respond adequately to medical, psychological, and pharmacologic management. Although a broad array of nonpharmacological 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.

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Appendix Glossary [Adapted from IASP Pain Terminology [1]]

Term	Definition
Allodynia	Pain due to nonnoxious stimuli (clothing, light touch) when applied to the affected area. May be mechanical (e.g., 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
Central Pain	Pain initiated or caused by a primary lesion or dysfunction in the central nervous system
Dysesthesia	Spontaneous or evoked unpleasant abnormal sensations
Eudynia	Symptom based pain provoked by an identifiable injury or noxious stimulus
Hyperalgesia	Exaggerated response to stimulus which is normally painful
Hypoesthesia	Decreased sensitivity of stimulation, excluding the special senses
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.
Pain threshold	The least experience of pain which a subject can recognize
Paresthesia	An abnormal sensation, whether spontaneous or evoked
Phantom pain	Pain from a specific site that no longer exists (e.g., amputated limb) or where there is no current injury
Referred pain	Pain that occurs in a region remote from the source