Chronic Pain Disease

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Abstract

Pain traditionally arises through nociceptive (tissue damage) or neuropathic (nerve injury) mechanisms. However, when pain persists beyond 3-6 months, this classification becomes insufficient. This review explores the pathophysiological transition from acute pain signal to chronic pain disease.

We describe how spinal sensitization (wind-up, NMDA receptor activation) represents the first step toward chronicization. In neuropathic pain, ectopic neuronal activity from aberrant sodium and calcium channel expression drives peripheral hyperexcitability. Critically, chronic pain involves profound central nervous system reorganization: cortical gray matter atrophy, descending control dysfunction, persistent glial activation, and cognitive-emotional circuit alterations. This leads to the concept of nociplastic pain—pain arising from altered nociception without clear tissue or nerve damage. Clinical consequences include loss of lesion-pain correlation and development of features (allodynia, generalized hyperalgesia) that transcend initial mechanisms.

Understanding chronic pain as a disease of the pain modulation system itself—rather than merely a persistent symptom—has fundamental implications for recognizing Pain Medicine as a distinct medical specialty requiring dedicated training and resources.

Keywords: chronic pain, central sensitization, nociplastic pain, pain chronicization, wind-up phenomenon, neuropathic pain, cortical reorganization

Pain can arise through two fundamentally different pathways: through normal activation of an intact sensory nervous system (nociceptive mechanism) or through dysfunction of the nervous system itself (neuropathic mechanism). However, when pain persists, these distinctions blur: the pain modulation system itself becomes pathological. This transition from "signal" to "disease" is what we explore here.

1 - Nociceptive Pain

1.1 - The Physiological Alarm System

The nociceptive system functions normally. Pain results from activation of tissue nociceptors by noxious stimuli (mechanical, thermal, chemical). It is a protective warning signal.

1.2 - Pathophysiology

Tissue injury releases a cascade of algogenic molecules: prostaglandins, cytokines (IL-1β, TNF-α), bradykinin, nerve growth factor (NGF), H+ ions, ATP. These mediators lower the activation threshold of nociceptors—this is called primary hyperalgesia. [1]

1.3. First Level of Amplification: Spinal Sensitization

When nociceptors send repeated volleys to the spinal cord, spinal neurons become progressively hyperexcitable: this is the wind-up phenomenon. NMDA receptors activate, amplifying the signal. [3] A zone of secondary hyperalgesia appears around the lesion.

Crucial point: This spinal sensitization is potentially reversible if the stimulus disappears quickly, but can also be the first step toward chronicization if it persists. The boundary between adaptive and pathological is crossed insidiously.

2 - Neuropathic Pain

2.1 - When the Messenger Becomes the Message

Neuropathic pain arises from a lesion or disease of the somatosensory nervous system itself (IASP definition). [1] It is no longer the territory sending alarm signals, but the neural network that is malfunctioning.

2.2 - Pathophysiology

Injured nerve fibers develop ectopic activity—spontaneous discharges independent of any stimulation. These discharges arise:

- At the lesion site (neuromas, demyelination)
- In the cell bodies of dorsal root ganglia
- More rarely, in the fibers themselves

Molecular mechanism

There is overexpression and redistribution of voltage-gated sodium channels (notably Nav1.7, Nav1.8), voltage-gated calcium channels (Cav2.2) on neuronal membranes. [1] These channels accumulate chaotically, rendering neurons hyperexcitable.

Associated abnormalities

- Ephaptic coupling: fibers "short-circuit" each other
- Catecholamine sensitization: fibers become sensitive to adrenaline, worsening with stress
- Aβ fiber sprouting: tactile fibers invade zones normally reserved for nociceptive fibers—touch becomes painful (allodynia)

2.3 - Spinal Amplification

Persistent peripheral afferent volleys induce spinal cord changes

- Hyperexcitability of second-order neurons
- Disinhibition: progressive loss of GABAergic and glycinergic interneurons (the system's brakes)
- Glial activation: microglia and astrocytes release pro-inflammatory cytokines (IL-1β, TNF-α), maintaining hyperexcitability [4]

This central sensitization progressively becomes structural: synaptic reorganization, loss of inhibitory interneurons, epigenetic modifications. [3,4] The system can no longer return to its initial state.

3 - Chronic Pain

3.1 - Beyond the Dichotomy

Whether pain began through a nociceptive mechanism (osteoarthritis, low back pain) or neuropathic mechanism (shingles, nerve compression), chronicization follows common pathways. After 3-6 months, the question "what is the cause?" becomes partially obsolete. The pain modulation system itself has become pathological.

This is expressed by the recent concept of nociplastic pain (IASP 2017): pain arising from altered nociception, without clear evidence of tissue damage [2] (which would define nociceptive pain) or lesion of the somatosensory nervous system (which would define neuropathic pain).

3.2 - Pathophysiology

3.2.1 - Cortical Reorganization

Neuroimaging reveals profound brain modifications that are associated with and may contribute to pain persistence.

- Gray matter atrophy: volume reduction in the anterior cingulate cortex, insula, dorsolateral prefrontal cortex [6]
- Alteration of the pain matrix: particularly hypoactivation of the prefrontal cortex
- Disruption of the default mode network: this network, active at rest, becomes dysfunctional—the brain can no longer "let go" of pain [5]

3.2.2 - Descending Disinhibition

Physiologically, the brain sends inhibitory commands to the spinal cord (descending serotonergic, noradrenergic, opioidergic controls). In chronic pain, this braking system becomes deficient, even paradoxically facilitatory. [3,5] The brain amplifies pain instead of attenuating it.

3.2.3 - Persistent Central Immune Activation

Microglia are activated and reactive astrocytes maintain a chronic neuroinflammatory state in the spinal cord and brain. [4]This “immune memory" of the central nervous system perpetuates pain.

3.2.4 - Cognitive-Emotional Entanglement

Psychological factors modulate pain through documented neurobiological pathways involving the limbic system and prefrontal cortex:

- Catastrophizing: rumination, amplification of perceived threat
- Kinesiophobia: movement avoidance due to fear of pain
- Hypervigilance: attention constantly focused on bodily sensations
- Comorbidities: anxiety, depression (70% of patients), sleep disorders

3.3 - Major Clinical Consequences

Through superimposition of pathological mechanisms, initially nociceptive pain develops:

- Allodynia (neuropathic mechanism)
- Generalized hyperalgesia, far from the joint (central sensitization)
- Partial response to antiepileptics/antidepressants ("neuropathic" treatment)

The lesion-pain correlation weakens considerably, and imaging becomes useless except to rule out red flags, but not to explain chronic pain. Pain becomes autonomous. It no longer requires a triggering stimulus. It self-perpetuates through central amplification loops, glial activation, cortical reorganization. It has become a disease of the nervous system, no longer merely a symptom.

5 - Conclusion

The nociceptive/neuropathic classification remains essential for understanding initial mechanisms and guiding early treatments. However, chronic pain disease transcends this dichotomy: it is primarily a pathology of the pain modulation and perception system—a pathological reconfiguration of the central nervous system itself.

Understanding this transition from signal to disease means accepting that chronic pain is no longer simply a symptom to "extinguish," but a complex disease requiring an integrative biopsychosocial approach. This is why Pain Medicine should be recognized as a specialty in its own right, identical to cardiology or internal medicine.

6 - References

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