Toward a Mechanism-Based Approach to Pain Diagnosis

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Abstract: The past few decades have witnessed a huge leap forward in our understanding of the mechanistic underpinnings of pain, in normal states where it helps protect from injury, and also in pathological states where pain evolves from a symptom reflecting tissue injury to become the disease itself. However, despite these scientific advances, chronic pain remains extremely challenging to manage clinically. Although the number of potential treatment targets has grown substantially and a strong case has been made for a mechanism-based and individualized approach to pain therapy, arguably clinicians are not much more advanced now than 20 years ago, in their capacity to either diagnose or effectively treat their patients. The gulf between pain research and pain management is as wide as ever. We are still currently unable to apply an evidence-based approach to chronic pain management that reflects mechanistic understanding, and instead, clinical practice remains an empirical and often unsatisfactory journey for patients, whose individual response to treatment cannot be predicted. In this article we take a common and difficult to treat pain condition, chronic low back pain, and use its presentation in clinical practice as a framework to highlight what is known about pathophysiological pain mechanisms and how we could potentially detect these to drive rational treatment choice. We discuss how present methods of assessment and management still fall well short, however, of any mechanism-based or precision medicine approach. Nevertheless, substantial improvements in chronic pain management could be possible if a more strategic and coordinated approach were to evolve, one designed to identify the specific mechanisms driving the presenting pain phenotype. We present an analysis of such an approach, highlighting the major problems in identifying mechanisms in patients, and develop a framework for a pain diagnostic ladder that may prove useful in the future, consisting of successive identification of 3 steps: pain state, pain mechanism, and molecular target. Such an approach could serve as the foundation for a new era of individualized/precision pain medicine. The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION)-American Pain Society (APS) Pain Taxonomy (AAPT) includes pain mechanisms as 1 of the 5 dimensions that need to be considered when making a diagnostic classification. The diagnostic ladder proposed in this article is consistent with and an extension of the AAPT.

Perspective: We discuss how identifying the specific mechanisms that operate in the nervous system to produce chronic pain in individual patients could provide the basis for a targeted and rational precision medicine approach to controlling pain, using chronic low back pain as our example.

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Key words: Diagnosis, low back pain, mechanism, target.

A mechanistic approach to address chronic pain has been actively promoted over the past few decades in an attempt to exploit the growing understanding of underlying pathological processes as a means to improve patient management. Medicine is obviously most impactful when defined...
mechanisms can be targeted with treatments that act specifically on those mechanisms. Conditions like diabetes and peptic ulcer disease were largely tamed with simple interventions when their mechanisms were recognized and could be directly addressed. As our understanding of disease in general has evolved from systems and organs to subcellular molecular pathways, opportunities for rational and precise treatment in a wide variety of conditions have grown substantially. In chronic pain, identification of molecular mechanisms has dramatically increased over the past few decades, however, there still remains a long journey to convert the effect of these discoveries into improved clinical practice. Patients are still largely managed on a “trial and error” basis, more influenced by which physician they see than any appreciation of underlying ‘pain mechanisms.’ Diagnostic tools commonly lack specificity for identifying the “pain driver” defined in terms of anatomical site, pathology, or pain mechanism, and treatment rarely targets such drivers. In consequence, clinical outcomes for chronic pain conditions remain disappointing, and prevalence and morbidity-related health care costs are unacceptably high, per data from the Global Health Data Exchange.77

To illustrate the problem, we take the most common chronic pain condition—chronic low back pain (cLBP)—and apply the current understanding of pain mechanisms to its presentation, diagnosis, and management. By doing so, we hope to summarize the state of scientific knowledge and also highlight the large discrepancy between the scientist’s mechanistic and the clinician’s pragmatic approach to chronic pain. On the basis of this analysis we introduce a new framework—a pain diagnostic ladder—as a first step toward a more structured and rational approach to mechanism-based pain medicine.

The Clinical Challenge of cLBP

Chronic pain is difficult to define—most definitions have evolved from consideration of pain that persists beyond the normal time of healing, typically taken as 3 months,107 which may reflect a transition from acute pathology-driven symptomatic pain to a persistent and often autonomous pain caused by changes in the peripheral and central nervous system (CNS). In consideration specifically of cLBP, all moving joints can cause pain if the joint is inflamed or has degenerated, and the spine, being a complex articulated structure of many discolateral and facet joints is no different. Because of the increasing mechanical burden of caudally located vertebrae and discs, lumbar and lumbosacral elements are particularly prone to the degenerative changes that occur in all humans over time.18 However, only a minority of people develop cLBP, and there is no strong correlation between cLBP and age or activity,73,77 which would be expected if degeneration alone were the prime pain driver. Other factors must be at play.

For one, it is important to consider whether chronic pain is autonomous of tissue injury or whether it reflects a chronically active disease, such as rheumatoid arthritis, spondyloarthritis, or ongoing nerve compression, which might be amenable to specific disease-modifying management, even long after pain onset. Chronic pain conditions include both categories; pain as a chronic disease of the nervous system and pain as a symptom of chronic peripheral disease, although distinguishing them is challenging and the 2 may coexist. In addition, it is becoming clearer that the development of cLBP may occur because of a combination of genetically-based susceptibility factors in the nervous and immune systems as well as local pathological risk factors; several human genes modifying the risk of pain chronification have been identified over the past few years.14 Furthermore, cLBP may not be one but several distinct conditions, which the commonly used loose term “degenerative low back pain” does not capture. Certainly the presentation of cLBP is very mixed, with wide anatomical and qualitative (eg, sharp vs dull, ongoing vs triggered) variability as well as the relationship to factors such as posture (lying, sitting, standing) and activity. Last, psychosocial factors play an important role in interindividual differences in chronic pain perception, and negative affect/depression as well as pain catastrophizing are thought to be major contributors to pain-related disability39,154 and are explored in other review articles in this issue of The Journal of Pain.40,146

There have been many attempts to classify cLBP to capture its causes; here we have divided cLBP into 3 major categories: anatomic, pathologic, and mechanistic.

Anatomic

The low back contains a large number of potential pain generators, including disc and facet joints, vertebral end

Figure 1. Chronic low back pain drivers. An illustration of pain drivers in chronic low back pain showing their anatomical locus and associated pathology, and the pain states they produce (vertebral column drawing done by Simmie Foster MD, PhD). Abbreviations: i, inflammatory; n, nociceptive; Nep, neuropathic.
In practice, it remains a major challenge to identify the specific contribution of each structure to the clinical presentation. The musculoskeletal clinical examination, with few exceptions as discussed in this article, has overall poor localizing value, and injections of local anesthetics, as in intra-articular facet joint injections or medial branch blocks, as well as provocative discography, remain controversial as diagnostic tools. In addition, magnetic resonance spinal imaging findings correlate poorly with the patient’s reports, and in many cases are unhelpful to identify a specific source of the pain. As pain becomes “centralized” (an initial peripheral trigger resulting in persistent alterations in the CNS) and in consequence, more widespread over time, it becomes increasingly more difficult and less relevant to identify the initial source. In some individuals there may never have been any peripheral trigger and the pain in these patients is considered to be an expression of central amplification because of increased excitation and reduced inhibition in central nociceptive circuits.

Pathologic

Although cLBP can result from several distinct pathological insults including trauma, infection, inflammation, and systemic disease such as cancer, the most cLBP sufferers are labeled as having “degenerative low back pain.” However, none of these pathological descriptors captures the basis of the patient’s pain. Chronic pain can be classified broadly into 4 pain states: nociceptive, inflammatory, neuropathic, and centralized/dysfunctional (Table 1). Nociceptive pain reflects activation of nociceptors (high threshold primary sensory neurons) by intense, typically in the case of clinical pain, mechanical stimuli. Inflammatory pain represents pain hypersensitivity in the presence of either sterile or pathogen-driven inflammation, and neuropathic pain results from damage to the nervous system. All 3 can contribute to cLBP and all 3 may occur in the presence of degenerative changes. Dysfunctional or centralized pain represents patients with chronic, often widespread pain conditions like fibromyalgia, where there is no noxious stimulus, no detectable inflammation, and no structural damage to the nervous system or any other tissue, and appears to result from abnormal pain amplification within the CNS. The contribution of central pain amplification in cLBP might play an important role in patients with pain disproportionate to minimal peripheral pathology (see Central Sensitivity Syndromes section), however absence of reliable biomarkers of central pain amplification make this a difficult positive diagnosis, one that is therefore typically made according to the absence of other positive pathological features.

Mechanistic

The utility in the clinic of a mechanistic classification of pain currently remains poor and is therefore infrequently used. Mechanistic approaches to the classification of cLBP attempt to highlight cellular mechanisms working at the level of sensory receptors in target organs, axons, and cell bodies of primary sensory neurons, or in the spinal cord and brain (Tables 2 and 3). Identifying such mechanisms, if possible, would provide an opportunity for specific targeting with pharmacological therapies that act on the identified mechanisms. Although basic science efforts have made remarkable progress in identifying some key molecular targets, a huge clinical challenge remains to identify these mechanisms from the individual pain patient.

Table 1. Pain States

<table>
<thead>
<tr>
<th>Pain State</th>
<th>Clinical Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptive</td>
<td>Evidence of noxious (mechanical) insult</td>
</tr>
<tr>
<td></td>
<td>Symptoms: pain localized to area of stimulus/joint damage</td>
</tr>
<tr>
<td></td>
<td>Signs: imaging—mechanical pathology/ altered joint architecture such that normal movements</td>
</tr>
<tr>
<td></td>
<td>will likely produce excessive forces sufficient to activate nociceptors</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Evidence of inflammation</td>
</tr>
<tr>
<td></td>
<td>1. Sterile</td>
</tr>
<tr>
<td></td>
<td>2. Infectious</td>
</tr>
<tr>
<td></td>
<td>Symptoms: redness, warmth, swelling of affected area</td>
</tr>
<tr>
<td></td>
<td>Signs: imaging (MRI, SPECT) signs of inflammatory changes, detection of pathogens/response to</td>
</tr>
<tr>
<td></td>
<td>antibiotics</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>Evidence of sensory nerve damage</td>
</tr>
<tr>
<td></td>
<td>Symptoms: burning, tingling or shock-like, spontaneous pain; paresthesias or dysesthesias</td>
</tr>
<tr>
<td></td>
<td>Signs: decreased pinprick* or vibration sense, and straight leg raise,* mechanical and cold</td>
</tr>
<tr>
<td></td>
<td>allodynia</td>
</tr>
<tr>
<td>Dysfunctional/centralized</td>
<td>Pain in the absence of detectable pathology</td>
</tr>
<tr>
<td></td>
<td>No identifiable noxious stimulus, inflammation or neural damage; evidence of increased</td>
</tr>
<tr>
<td></td>
<td>amplification or reduced inhibition</td>
</tr>
</tbody>
</table>

Abbreviation: SPECT, single-photon emission computed tomography.

NOTE. The 4 categories of nociceptive, inflammatory, neuropathic, and dysfunctional/centralized pain, and their clinical presentation. Note that none of the diagnostic criteria are highly specific, and there is no gold standard for diagnosing these conditions. Pain states are not mutually exclusive, and coexistence of more than 1 is probably the rule rather than the exception.

*Most specific
Table 2. General Pain Mechanisms

<table>
<thead>
<tr>
<th>General Pain Mechanism</th>
<th>Clinical Diagnostic Criteria</th>
<th>Specific Treatment Examples</th>
<th>GABA-Pentinooid</th>
<th>AED</th>
<th>AD</th>
<th>Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptive transduction</td>
<td>Proportionate pain in response to identifiable noxious stimulus</td>
<td>Removing mechanical stimulus (eg, decompression of nerve)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Peripheral Sensitization</td>
<td>Primary hyperalgesia due to decreased transduction threshold of nociceptor terminal</td>
<td>Anti-inflammatory (eg, NSAID, coxibs); immunosuppressant</td>
<td></td>
<td>X</td>
<td></td>
<td>Possibly X</td>
</tr>
<tr>
<td>Ectopic activity</td>
<td>Spontaneous pain in the absence of obvious trigger; relieved by local nerve block</td>
<td>Na,- channel blockers</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Central sensitization</td>
<td>Secondary hyperalgesia; temporal summation; allodynia</td>
<td>NMDA antagonists (eg, ketamine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central disinhibition</td>
<td>Secondary hyperalgesia; allodynia</td>
<td>GABA-A subunit agonists; dual amine uptake inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AED, antiepileptic drugs; AD, antidepressants; NSAID, nonsteroidal anti-inflammatory drug; coxib, selective COX-2 inhibitor; VA, valproic acid; TPM, topiramate.

NOTE. More than 1 mechanisms may be at play in any given pain syndrome and no mechanism is specific to a particular pain state. It is currently impossible to distinguish clinically between central sensitization and disinhibition. Several of the proposed specific treatment examples are not in clinical use (eg, Nav-specific or GABA A receptor-specific antagonists). Note the low specificity of currently used medications for a single mechanism.

Table 3. Specific Pain Targets

<table>
<thead>
<tr>
<th>Selected Specific Pain Mechanisms</th>
<th>Preclinical Manifestation</th>
<th>Specific Clinical Manifestation</th>
<th>Molecular Target</th>
<th>Genetic Validation</th>
<th>Specific Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased NGF synthesis</td>
<td>Nociceptor activation at lowered heat threshold</td>
<td>Peripheral sensitization</td>
<td>TrkA (NGF receptor); TRPV1</td>
<td>HSAN IV HSAN V</td>
<td>anti-NGF A8 (phase 3); TrkA R antagonist (phase 2)</td>
</tr>
<tr>
<td>NMDA receptor phosphorylation</td>
<td>Increased postsynaptic activity</td>
<td>Pain amplification</td>
<td>NMDA receptor</td>
<td>No</td>
<td>NMDA receptor antagonist (eg, ketamine)</td>
</tr>
<tr>
<td>Excitatory transmitter release</td>
<td>Increased postsynaptic activity</td>
<td>Pain amplification</td>
<td>Ca(v)2S-1</td>
<td>No</td>
<td>Gabapentinoids</td>
</tr>
<tr>
<td>Na,1.7 hyperexcitability</td>
<td>Increased nociceptor firing</td>
<td>Paroxysmal extreme pain disorder; primary erythromelalgia</td>
<td>Na,1.7</td>
<td>Paroxysmal extreme pain disorder; primary erythromelalgia</td>
<td>Na,1.7 antagonist (phase 2)</td>
</tr>
<tr>
<td>Spinal interneuron degeneration</td>
<td>Decreased inhibitory transmission</td>
<td>Pain amplification</td>
<td>GABA A receptor</td>
<td>No</td>
<td>Gaba A receptor subtype selective agonist</td>
</tr>
<tr>
<td>TRPA1 sensitization</td>
<td>Increased nociceptor firing</td>
<td>Familial episodic pain syndrome</td>
<td>TRPA1</td>
<td>Familial episodic pain syndrome</td>
<td>TRPA1 antagonist</td>
</tr>
</tbody>
</table>

NOTE. Molecular targets identified in preclinical models and sometimes rare human genetic mutations. Clinical identification of these molecular mechanisms remains the most challenging and least developed step on the pain ladder, because of the absence of any diagnostic tools/biomarkers. Some specific treatment options are available or in clinical development, but identification of these mechanisms in patients to select specific treatments remains the biggest challenge.
phenotype and to then target the molecular mechanism with a specific treatment. Nevertheless, this strategy remains as we will argue, the most promising for individualized diagnoses and treatment, and therefore continues to deserve attention even if it is not attainable at present.

Pain States

Pain is a multimodal, complex experience involving multiple neural sites, including peripheral nerves, the spinal cord, and higher brain centers. The specific receptive properties of thinly myelinated (Aδ fiber) and unmyelinated (C-fiber) nociceptors are determined by membrane-bound transducing ion channel receptors, which are gated by temperature, chemical stimuli, or mechanical forces, and upon activation transduce an external stimulus into a change in membrane potential by opening a sodium/calcium or closing a potassium channel. Examples of transducer receptors are TRPV1 for heat, acid-sensing ion channels for free protons and Piezo-type mechanosensitive ion channel component 2 for mechanical sensation. The modifiability of the synaptic contact between nociceptors and spinal cord dorsal horn neurons, and further modulation of nociceptive signals in the CNS by immune cells, local interneurons, descending pathways from the brain and brainstem, and cognitive/affective components, together determine the complex and dynamic, individual pain phenotype.

The following sections, and Tables 1–3 highlight major mechanisms underlying nociceptive, inflammatory/infectious, and neuropathic pain and their known or postulated occurrence in common clinical scenarios—with emphasis on cLB and without inclusion of psychosocial influences, which are certainly important, but beyond the scope of this review.

Nociceptive Pain

Nociceptive pain in a clinical setting is the result of activation of high threshold mechanoreceptors by increased mechanical forces (eg, joint capsule stretch or impingement due to destruction of normal joint architecture). In the healthy spine, the 2 facet joints carry approximately one-third of the total load at a given spinal level (the rest going through the disc) but this can increase to 70% in the presence of severely degenerated discs. In an experimental setting, injecting saline into a healthy lumbar facet joint—thus increasing pressure—causes pain, and neurophysiologic recordings from facet joints confirm activation of high-threshold fibers upon joint extension. Although joint-associated structures, including fat pads, ligaments, joint capsules, synovium, and subchondral bones, are richly innervated by nociceptors, and are therefore all potential pain generators, not all will be exposed to noxious mechanical forces, even in cases of severe joint degeneration. Often, however, degeneration is relatively mild compared with pain severity, so that local inflammation likely also plays a major role in the generation of cLB.

Inflammatory Pain

Inflammatory pain results from the activation and sensitization of nociceptors by inflammatory mediators, caused for example, by an inflammatory synovial response to cartilage damage of the facet joint. Elevated levels of inflammatory cytokines (eg, interleukin [IL]-1 or IL-6), as well as increased capsular vascularization and inflammatory cells are present in degenerate facet joints. Because of the close proximity of the facet joint to the dorsal spinal root and dorsal root ganglion, local inflammation in the facet could spread from the joint to directly affect nearby neuronal cells and axons, causing pain with a radicular distribution. For example, patients with lumbar canal stenosis show higher pain scores and disability if IL-1β levels are elevated in the facet joints. IL-1β can induce cyclooxygenase (COX)-2 in neurons and the production of matrix metalloproteinases in synovial fibroblasts, the enzymes responsible for cartilage degradation, illustrating a molecular coupling between joint inflammation and subsequent degeneration.

Pain due to degenerative disc disease represents a quite different process from that in facet joints, because of the lack of a synovial structure in the disc, which is necessary to cause the inflammatory picture typical of osteoarthritis. The fully developed nucleus pulposus remains vessel-free and isolated from immune exposure, and therefore is capable of invoking an autoimmune response and subsequent inflammation upon release into an immunogenic environment. Several inflammatory markers (eg, IL-1α, tumor necrosis factor [TNF]-α, transforming growth factor-β) have been found in herniated discs, and increased levels of discogenic cytokines correlate with increased pain levels. A distinct but possibly related mechanism is the ingrowth of nociceptive fibers from the outer ring of the annulus fibrosis into the inner ring and even into the nucleus pulposus, which has been reported in the degenerate disc and is associated with increased lower back pain.

Tissue damage or inflammation results in local release of the intracellular content of injured cells and of inflammatory signaling molecules from immune cells, such as prostaglandins, growth factors (eg, nerve growth factor [NGF]) and cytokines (IL-6, IL-1β, TNF-α). Although some of these agents directly activate transducer molecules on nociceptor terminals (eg, ATP acting on P2X3 receptors), inflammatory mediators also lead to post-translational and transcriptional changes of transducers (eg, NGF results in decreased threshold and increased expression of the TRPV1 channel).

When transducing ion channels are activated by adequate stimuli, voltage-gated sodium channels expressed by nociceptors, such as Na+, are responsible for amplifying the initial transducer current and triggering an action potential, and therefore play a key role in determining the excitability and signaling of sensory neurons. Inflammatory mediators can change the trafficking, cell surface expression, and gating properties of these channels, resulting in increased excitability.
Peripheral inflammation induces not only changes in the nociceptor but also in the CNS. For example, there is a marked increase of COX-2 in spinal cord neurons after peripheral inflammation in response to systemically acting cytokines such as IL-1β and IL-6, and this seems key to the development of mechanical hyperalgesia in the inflamed anatomical area, whereas the local expression of COX-2 at the inflamed site drives heat hypersensitivity. COX-2 inhibitors with well documented blood-brain barrier penetration (eg, celecoxib) might therefore be more efficacious in conditions with marked mechanical inflammatory pain hypersensitivity due to such a central COX-2 induction.

**Infection**

Infection and the subsequent immune response it generates represent a distinct and important pain mechanism. The local host response to pathogens with invasion of inflammatory cells and subsequent synthesis of proinflammatory cytokines like TNF-α, interleukin IL-1β, and IL-6 can directly activate and sensitize nociceptors in a fashion similar to that which occurs in tissue damage-associated inflammatory conditions. However, only recently has it been shown that gram-negative and gram-positive bacteria directly activate nociceptors, independent of the immune response.

Interestingly, 31% of 140 patients with no infectious symptoms in the previous 6 months and severe sciatica, tested positive for gram-positive infection on serological testing, and 53% of 36 patients who underwent microdiscectomy had positive disc cultures, with the most common pathogen being Propionibacterium acnes. Similarly, in 61 patients who underwent discectomy, 46% with Modic type I changes on lumbar magnetic resonance imaging (MRI; implying inflammation/edema of the vertebral end-plate) were found to have a discogenic infection, and a strong correlation was found between the presence of anaerobic disc infection and development of Modic type I changes. A recent randomized trial of 162 patients with cLBP and Modic type I changes showed statistically significant improvements in pain and disability at 1 year when treated with 100 days of amoxicillin versus placebo. The surprising notion that an antibiotic may effectively work as an analgesic in a subgroup of chronic pain patients highlights the paramount importance of a mechanistic approach to cLBP. To do this, we need accurate biomarkers of mechanisms, including those for detection of the presence of ongoing pathogen infection.

**Neuropathic Pain**

Peripheral nerve damage can result either from systemic diseases causing polyneuropathy and mononeuropathy or to a local insult such as trauma, compression, and inflammation causing mononeuropathy or radiculopathy. For classic lumbar or cervical radiculopathy (clinically defined as pain, weakness, or numbness in a myotomal/dermatomal distribution), our understanding is shifting from an etiology defined simply according to the degree of mechanical root compression (eg, from a herniated disc or hypertrophied facet joint), to recognition of a more complex interplay between a mechanical compressive insult and its associated inflammatory phenomenon, such as chemical factors released from injured disc material or an inflamed facet joint. This insight derives from several clinical observations: relief of mechanical compression using discectomy or laminectomy does not always result in immediate symptom relief; the degree of mechanical compression does not correlate well with the severity of clinical symptoms; conservative therapies targeted at reducing inflammation and musculoskeletal remodeling can be successful even when radiological compression persists; direct nerve root stimulation can cause dysesthesia, numbness, and motor loss, but not pronounced pain; and nucleus pulposus material, introduced into the epidural space at a distance from the nerve root, can induce nerve fiber degeneration without any compression.

In recognition of the prominent inflammatory component in neuropathic pain, several inflammatory markers have been identified as potential therapeutic targets. As an example, TNF-α is elevated in the periradicular epidural fat in patients with radiculopathy from herniated disc disease and infusion with a TNF-α neutralizing antibody is reported to result in pain reduction for up to 3 months in patients with severe sciatic pain due to disc herniation. In a randomized trial of patients with acute radicular leg pain due to disc herniation, 2 subcutaneous treatments with the anti-TNF-α antibody showed a small but significant improvement in leg pain over 6 months, favorable outcomes regarding back pain and disability, and a decreased rate of surgery at a 3-year follow-up. Although the long-term benefit of TNF-α antibodies remains controversial and this treatment has not entered common clinical practice yet, these data suggest that chronic inflammation may be an important component for development of cLBP or radiculopathy.

Nevertheless, radiculopathy does not generally occur in the complete absence of mechanical compression, so that there is likely a complex interplay between mechanical and inflammatory factors needed to cause the clinical syndrome. In cases of mechanical compression causing severe pain unresponsive to conservative therapy, if additional signs of neural compression occur, such as bowel or bladder impairment or an evolving neurological deficit—such as worsening weakness of the affected area, surgical decompression may be vital to functional recovery and pain reduction.

**Central Sensitivity Syndromes**

Central sensitivity syndromes (CSS), in which no well defined peripheral or central disease process can be found are thought to represent a primary dysregulation of the CNS leading to pain amplification, and are sometimes termed centralized pain or central sensitization. Examples include somatic pain syndromes such as fibromyalgia and temporomandibular disorder, as well as visceral pain syndromes like interstitial cystitis and...
irritable bowel syndrome, and possibly cognitive impairments such as chronic fatigue syndrome. Attempts to diagnose these disorders on the basis of their “central” component include self-reported symptom questionnaires such as the Central Sensitization Inventory and Fibromyalgia Criteria and Severity Scales, which have the patient evaluate and grade a wide array of symptoms, including somatic and visceral pain, mood, energy, sleep, and cognitive function, among others. Although some of the pain symptoms occurring in these conditions can likely be explained by the physiologically well-defined phenomenon of activity-dependent central sensitization described in the Spinal Mechanisms: Sensitization and Disinhibition section (that is an increased responsiveness of CNS nociceptive neurons to afferent input due to increased excitation and reduced inhibition in defined circuits), the diffuse cognitive and affective symptoms that are part of CSS are difficult to explain by a unified disease process/mechanism. Nevertheless, CSS for somatic and for visceral pain seem to be at least partially dependent on continuous peripheral input, as shown by the effects of injection of local anesthetic, which can reduce remote pain sensitivity (secondary hyperalgesia, see below) in fibromyalgia patients, as well as visceral and cutaneous hypersensitivity in irritable bowel syndrome patients. In contrast, the conditions of low back pain, neck pain, and radiculopathy, most if not all appear to have an initial peripheral disease process, which over time can result in a more widespread pain phenotype outside of the damaged area. The extent to which cLBP includes an element of mechanistic overlap with CSS is unknown because there is no specific biomarker or treatment for CSS, but this is an area of growing interest.

Although much work is required to understand the pathophysiology of these widespread pain conditions, the most clinically relevant aspect might be that the response generally of these patients to treatment is poorer and they have worse surgical outcomes, perhaps because the wrong drug target or pathological locus is selected.

**Pain Mechanisms**

**Nociceptive Transduction**

Nociceptive transduction represents the physiological conversion of an intense (noxious) thermal, mechanical, or chemical stimulus into activity in a nonsensitized nociceptor. Although this mechanism can contribute to chronic pain in specific settings (eg, damage to a joint resulting in abnormal mechanical forces), it rarely is the sole contributor in chronic pain states.

**Peripheral Sensitization**

Peripheral sensitization constitutes a decreased threshold and increased responsiveness of nociceptors as a result of post-translational changes in and altered trafficking of transducer receptors (eg, TRPV1) and ion channels (eg, Na, channels). This is caused by local inflammatory mediators, and results in pain hypersensitiv-
noxious stimuli. Heterosynaptic facilitation in the spinal cord differs fundamentally from homosynaptic changes in that it takes place at synapses not restricted to the initiating nociceptor input. For example, in healthy human volunteers, subcutaneous injection of capsaicin produces several minutes of severe pain restricted to the site of injection (the noxious conditioning stimulus) and this is followed by tactile allodynia in the areas around the site of injection, and pinprick hyperalgesia in an even larger area. These symptoms result from the novel functional recruitment of Aβ and Aδ fibers into the nociceptive pathway by strengthening synapses between the fibers and nociceptive neurons in the spinal cord dorsal horn, by heterosynaptic facilitation. They are clinically referred to as secondary hyperalgesia, and many neuropathic pain conditions. Principal molecular mechanisms of this form of central sensitization are the activation of several protein kinases by the neurotransmitter glutamate and various neuropeptide transmitters, which lead to post-translational and transcriptional changes in postsynaptic receptors (eg, the NMDA receptor). The specific circuitry underlying central sensitization is beginning to emerge. That central sensitization is a major driver of neuropathic pain is supported by the action of drugs that reduce central excitability, including gabapentanoids (eg, gabapentin and pregabalin), tricyclic antidepressants (eg, amitriptyline), SNRIs (eg, duloxetine), and NMDA antagonists (eg, ketamine). The extent to which a persistent and autonomous central sensitization type of phenomenon can be set up in patients with cLBP but without damage to the peripheral nervous system or CNS is uncertain, as are the circuits involved and the mechanism responsible.

Temporary summation as a surrogate for central sensitization can be measured clinically by applying repetitive heat or mechanical stimuli. There might be a correlation between the intensity of the initial conditioning injury and the degree of secondary hyperalgesia as well as time to recovery, as shown in patients with cervical whiplash injury who develop a higher degree of sensory disturbance, lowered pain thresholds, and prolonged symptoms if the initial whiplash injury pain was severe as opposed to mild or moderate. This raises the question whether there might be an advantage in treating more severe patients early and aggressively.

**Disinhibition**

In addition to the strengthening excitatory synapses in the spinal cord, loss of inhibition by decreasing GABAergic and glycinergic tone also contributes to central hyperexcitability, and can be produced by peripheral nerve lesions. Increasing spinal inhibition with intrathecal gamma aminobutyric acid (GABA) or by activation of inhibitory interneurons results in an antinociceptive effect, while blocking inhibitory transmission (eg, by selective ablation of glycinergic dorsal horn interneurons), leads to lowered pain thresholds and the development of hyperalgesia and tactile allodynia. Mechanisms of disinhibition include reduced descending inhibitory control, loss of GABAergic or glycinergic interneurons through cell death, reduced GABA or GABA-synthesizing enzyme (eg, glutamate decarboxylase), and altered properties of GABA_A receptors, glycinergic receptors, and cation-chloride cotransporters. Restoring spinal cord inhibition by, for example, subtype-specific GABA receptor agonists, may offer the opportunity to reduce pain without limiting side effects like sedation.

**Contribution of the Immune System**

Reciprocal signaling between neurons and immune cells in the CNS has been identified as a possible key contributory mechanism to some chronic pain conditions. After peripheral nerve injury, a cocktail of neuronaally-derived mediators activate spinal microglia, which transition to a state of reactive gliosis and release molecules causing astrogliosis and invasion of T cells into the spinal cord. Subsequent release of immune mediators from microglia can enhance synaptic neurotransmission, presynaptically by increasing glutamate release or postsynaptically by AMPA and NMDA receptor modulation. Astrocytes contribute indirectly to increased synaptic glutamate levels and nociceptive hypersensitivity by downregulation of the spinal astrocyte glutamate transporters after peripheral nerve injury.

Other cytokines (eg, TNF-α, IL-1β, and IL-6) contribute to a disinhibition of spinal pain networks by reducing the release of GABA and glycine from interneurons and inhibitory descending projections. In cLBP patients, activation of microglia can be detected in the thalamus, pre- and postcentral gyri, and paracentral lobule using functional imaging (positron emission tomography/MRI) and the radioligand 11C-PBR28, a marker for activated microglia and reactive astrocytes. This biomarker might prove useful as a diagnostic tool, identifying subsets of patients whose pain is driven by non-neuronal cells in the CNS, and who may benefit therefore, from treatment targeting central immune cells.

**Supraspinal Mechanisms**

In chronic pain patients, structural changes such as a decrease in neocortex gray matter have been detected, as well as changes in excitatory and inhibitory transmitters and in functional connectivity. How these changes relate to the cognitive, sensory, and emotional pain experience, and if these changes are dependent on the original peripheral or central insult is uncertain, although some of these changes (eg, gray matter volume loss) seem to be reversible after pain treatment.
observed by applying mechanical pressure, which evokes muscle pain at a significantly higher intensity, in a wider distribution and for significantly longer time than in control subjects. This corroborates with functional brain MRI imaging, where cLBP patients show widespread activity in response to mechanical pressures at levels that in control subjects only evoke focal somatosensory cortex activation.

The Challenge of Applying an Understanding of Pain Mechanisms Into Clinical Practice

Can the traditional clinical methods (Table 4) of history, examination, and investigation inform the clinician about probable pain mechanism(s) and their locus, in the absence of information about a patient’s genotype, transcriptional, cellular, and neurophysiological status? Can clinicians appreciate anatomically the predominant pain generator, pain state, and the underlying mechanism(s)?

Efforts to ascertain information about mechanisms using a symptom-oriented approach have resulted in several patient questionnaires, most of them with the stated focus only of identifying a neuropathic component within a given pain syndrome, such as cLBP. The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain has recommended 5 questionnaires to screen for neuropathic pain: ID Pain, Leeds Assessment of Neuropathic Symptoms and Signs, PainDETECT questionnaire, Douleur Neuropathique 4, and Neuropathic Pain Questionnaire, with the latter 2 having the largest evidence base. The validity of questionnaires is hampered by lack of any diagnostic gold standard for neuropathic pain in a patient, such that the questionnaires define the syndrome, rather than the syndrome being revealed by the questionnaire. Other problems arise from the coexistence of neuropathic pain with other pain states in many patients and the poor cross-cultural validity of translated questionnaires.

Some questionnaires rely entirely on patient-reported symptoms, which are convenient but may distort the signal to noise ratio, whereas others require a detailed sensory examination done by a clinician—a challenge in a busy clinical practice. In the end, the most important question will be whether such approaches are sensitive and specific enough for diagnosis and can help with informed treatment choices.

On the basis of the 5 questionnaires mentioned, the most common signs and symptoms of neuropathic pain are considered mechanical and temperature-evoked allodynia, numbness to all modalities, burning/tingling/electric shock-like paresthesias, absence of persistent pain, and presence of intermittent pain attacks. An assumption is that these symptoms reflect the neuropathic pain mechanisms discussed previously, but their specificity is poor. For example, tactile allodynia could be caused by recruitment of low-threshold A-β fibers involved in somatosensory cortex activation.

Table 4. Common Diagnostic Testing for Patients With Chronic Low Back Pain

<table>
<thead>
<tr>
<th>DIAGNOSTIC TEST</th>
<th>INTERPRETATION</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Burning/tingling/electric shock like paresthesias = neuropathic pain</td>
<td>Poor specificity</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Lumbar radiculopathy/sciatic nerve irritation</td>
<td>Coexistence of more than 1 pain state</td>
</tr>
<tr>
<td>Dermatomal sensory loss/myotomal deficit</td>
<td>Root compression/damage</td>
<td>Different mechanisms can produce same symptoms</td>
</tr>
<tr>
<td>Musculoskeletal maneuvers (eg, facet loading, sacroiliac joint and hip maneuvers, low back palpation)</td>
<td>Anatomic localization of pain driver</td>
<td>No gold standard</td>
</tr>
<tr>
<td>Investigations</td>
<td>Presence/absence of neuropathy or radiculopathy</td>
<td>Unable to distinguish between L4, L5, S1, root, or sciatic nerve</td>
</tr>
<tr>
<td>QST</td>
<td>“Sensory fingerprint” indicative of pain mechanism</td>
<td>Significant dermatomal/myotomal overlap</td>
</tr>
<tr>
<td>MRI imaging</td>
<td>Degenerative changes judged as causative of pain syndrome</td>
<td>Multiple structures are simultaneously stimulated</td>
</tr>
</tbody>
</table>

Abbreviations: SLR, straight leg raise; NCS, nerve conduction study; EMG, electromyogram.

NOTE. Examples of commonly used diagnostic tools including patient’s symptoms, examination findings, and ancillary testing with clinical interpretations and short-comings.
mechanoreceptive fibers due to central sensitization in the spinal cord or spinal disinhibition. Similarly, burning pain may reflect activity somewhere in the pathway dedicated to heat sensation, but where? Is it due to activation of heat nociceptors by body temperature after peripheral sensitization, ectopic activity in injured heat nociceptors, or disinhibition of heat pain projection neurons in the spinal cord? It is clearly difficult to infer mechanism from positive symptoms, although negative symptoms such as numbness generally reflect disruption of the nervous system in a way that respects anatomy.\(^\text{129}\)

For certain pain conditions, a distinctive “sensory fingerprint” may give useful insight into pathogenesis. For example, distinct symptom patterns or ‘clusters’ have been identified in patients with painful radiculopathy versus axial low back pain (see the section on Quantitative Sensory Testing [QST]), although clinical signs seem to be more reliable than symptoms. Decreased pinprick sensation was found to be the best discriminator between axial low back pain and radicular pain (compared with a clinical ‘gold standard’) and 3 parameters (response to pinprick, straight leg-raising test, vibration sense) could reliably discriminate between painful diabetic neuropathy, postherpetic neuralgia, and radicular lower back pain.\(^\text{129}\) Therefore, questionnaires, although convenient to administer, probably cannot substitute for a focused physical examination, and should be used with caution for making clinical diagnoses by themselves.

### Clinical Examination

Experimentally, the presence of secondary hyperalgesia, temporal summation, and tactile allodynia are all considered signs reflective of central sensitization.\(^\text{118,134}\)

In the clinical setting however, mechanistic identification is challenging. Typically, a clinical examination tries to localize a pathology to a distinct anatomical structure. The straight leg- and crossed straight leg-raising test is a reliable test for painful radiculopathy or sciatica, and shows relatively high sensitivity and specificity, respectively.\(^\text{125,129}\) but other physical tests (motor deficit, muscle wasting, impaired reflexes, sensory deficits) are rather unreliable.\(^\text{147}\) Similarly, physical examination for other components of cLBP, including musculoskeletal palpation and manipulation, or provocative tests for facetogenic and sacroiliac pain, show poor diagnostic validity and interobserver reliability.\(^\text{70,126}\) In summary, standard clinical examination techniques, although helpful to screen for serious pathology such as spinal cord compression or cauda equina compression, perform poorly in identifying the anatomic source of cLBP and even more so, the mechanistic nature of low back pain and radiculopathy.

### QST

QST is currently used as a research tool but is impractical for standard clinical practice. Standardized sensory testing algorithms and a modality-specific evaluation of stimulus-evoked pain may add value to nerve conduc-tion studies, which only examine large nerve fibers, and assist in conclusions as to underlying mechanisms.\(^\text{10}\) For example, secondary hyperalgesia can be systematically assessed in patients with knee osteoarthritis, where lower pressure pain thresholds at remote sites from the diseased joint correlate with poorer outcome for total knee replacement.\(^\text{109}\) Hyperalgesia to cold and heat stimuli in oxaliplatin- but not cisplatin-induced neuropathy, points to distinct mechanisms of nerve damage of the 2 drugs, which might drive treatment choice in the individual patient.\(^\text{9}\) For axial low back pain, several sensory clusters with potentially distinct underlying mechanisms have been identified.\(^\text{46}\) For example, one cluster characterized by pressure tenderness of paraspinal muscles and a dull and aching pain quality, was interpreted as reflecting nociceptive pain of musculoskeletal structures, possibly driven by muscle spasm and mechanical degenerative change in the facet joint and disc. Another cluster of patients had pain in a similar distribution, but characterized by severe pain attacks precipitated by routine movements, which may be due to inflammation in facet joints or discs resulting in sensitization of the nerve fibers. Yet another cluster was defined by burning and pricking sensations, possibly reflecting a neuropathic etiology.\(^\text{46,48}\) Such symptom clusters present an interesting research opportunity to see whether they may be indicative of distinct underlying pain states (nociceptive, inflammatory, neuropathic) or mechanisms (eg, peripheral or central sensitization), although even within a seemingly homogenous group of patients with cLBP multiple different mechanisms are likely to be at play, creating complex and overlapping phenotypic symptom clusters. Biological biomarkers may be required to tease them out.

Correlations have been sought between QST parameters and analgesic response to improve therapy choice for the individual patient. As an example, baseline heat pain thresholds predicted response to opioid treatment but not to amitriptyline in patients with postherpetic neuralgia.\(^\text{41}\) However, because of the heterogeneity of conditions and outcomes, no robust QST parameter for reliable analgesic response prediction has been identified so far.\(^\text{65}\) Similarly, because of the large variability in the pain phenotype of patients with cLBP, identifying a sensitive/specific and time-efficient diagnostic QST test in a clinical setting may not be feasible.

### Imaging

Imaging cLBP patients is considered a key component for establishing diagnosis. Yet, as discussed earlier, the ubiquitous nature of degenerative changes in the spine makes any correlation between symptoms and imaging poor.\(^\text{79,103,129}\) Although imaging can rule out serious pathology (eg, tumors, spinal infection, fractures, cauda equina syndrome), routine computed tomography and MRI imaging of cLBP patients increased 300% between 1994 and 2005 without improved clinical outcomes.\(^\text{103}\) Nevertheless, as our understanding of cLBP mechanisms progresses, the role of imaging is likely to evolve. An annular tear might be,
for example, the trigger for an immunogenic response, ingrowth of nociceptors into the inner area and hence the source of discogenic, nociceptive pain; Modic changes in vertebral endplates are associated with cLBFP and in some cases possibly represent infection; discs with adjacent Modic type I changes show higher levels of inflammatory markers (e.g., TNF-α) and increased nerve fiber density.12,144,164 Recent studies using T2* sequences to quantify features of disc health have shown a better correlation between disc degeneration and functional spinal mechanics than traditional MRI techniques.42 Single-photon emission computed tomography is being used more widely to identify activity (assumed to be a marker of inflammation/possible nociceptor sensitization) in facet and sacroiliac joints and several studies have found that patients with single-photon emission computed tomography-positive facet arthropathy had better outcomes with intra-articular lumbar facet joint injections than patients who underwent medial branch blocks (the nerve supplying the facet joint).1,121

Targeting Mechanisms With Interventions

Pharmacological

Pharmacological pain relief in clinical practice often represents an empirical journey up an analgesic ladder (nonsteroidal anti-inflammatory drugs, “neuropathic” agents, other adjunct medications including antiepileptic drugs, and finally opioid medications), and is more often dictated by patient-centered factors (including medical history, tolerance of side-effects, compatibility with other medications), rather than targeting a pain mechanism. Because of the recognized difficulties in identifying mechanisms clinically, one strategy is to postulate the mechanism on the basis of pharmacological response (ex juvantibus)—give a drug, assess its efficacy, and for the successes, postulate a likely mechanism. For example, if a patient improves after being prescribed gabapentin or an anti-inflammatory agent, does this reflect a neuropathic or inflammatory pain state? As indicated in Table 2, most of the currently used medications have broad and complex mechanisms of action, often acting at several sites and molecular targets, and hence clinical response rarely allows postulation of a specific pain mechanism.

Physical and Psychological Treatment

Physical back pain management strategies can be divided into passive therapies (e.g., manipulation and massage) and active therapies such as patient-directed exercise, stretching, and core-stability techniques. There is some evidence for such therapies working in the short- to medium-term.86,139 Clearly, they do not work for every patient and there are a host of factors that influence their efficacy above and beyond the pain mechanism (e.g., placebo-responder status, premorbid condition and fitness level, age, motivation, and compliance). There is debate about how these techniques influence cLBFP and the evidence for or against the use of physical therapy at least as a stand-alone treatment is weak.88,89

As part of a multimodal approach to pain treatment, psychological interventions like cognitive behavioral therapy and treatment of negative affect appear useful for patients suffering from depression and pain catastrophizing,39 and are explored in dedicated reviews in this issue of The Journal of Pain.40,146

Spinal Injection

Spinal injections (local anesthetics with or without steroids) have increased many fold over the past 10 to 15 years.152 Although some of these injections appear to have clinical benefit for select patients for weeks to a few months, their clinical use remains controversial.28,72,131,132 and cynics might argue that it has become an industry driven more by financial than health-outcome factors. What do injections teach us of mechanisms? There are some observations that are difficult to explain. For example, the clinical response to an injection with local anesthetic often far outlasts the pharmacological action of the injected agent; cLBFP patients have lowered pain thresholds to mechanical, heat, chemical, and electrical stimulation, in the lower back and at more distal sites, and functional brain imaging and magnetic encephalography reveals an increase in the gain of central processing after peripheral stimuli in lower back pain patients.58,61 How then can the temporary numbing of a localized peripheral site, with or without the addition of steroids, result in long-lasting and profound changes in pain perception? One possibility is that a stable “pathological pain network” is established in the CNS of chronic pain patients and this is dependent on continuous input from peripheral sites to maintain it; when this generator is temporarily removed, the system reverts to lower amplification levels.63 Alternatively, locally administered anesthetics could have systemic effects. Lidocaine infusions are routinely used in pain clinics for widespread pain syndromes, and again pain relief outlasts the pharmacological activity of lidocaine on sodium channels by weeks. This might be related to off-target effects of lidocaine, like its anti-inflammatory properties,20 including its ability to decrease cytokine production of activated microglia in the CNS.60 Another important explanation is the placebo, which pain medicine is particularly prone to,74 and interventional procedures result in higher placebo responses than pharmacological therapies.105

A further question is how to interpret an analgesic response (or a failure to respond) after a local injection. What does this inform us about the location of the primary pain generator or the underlying pain state? A positive response to a facet joint medial branch block might be, for example, due to decreased afferent information from a primarily osteoarthritic/inflamed facet joint, decreased neuropathic pain from a mechanically compressed medial branch nerve or neither—the pain driver may be more proximal in the dorsal root, the dorsal root ganglion, or even the CNS, and normal input from the
medial nerve is perceived as pain. Also, in analogy to surgical rhizotomy, which can cause chronic denervation pain, could radiofrequency lesioning of medial nerve branches contribute to chronic neuropathic pain in susceptible patients?

**Surgical**

Perhaps the most controversial topic in the management of chronic back pain is the role of surgery, best exemplified by the ‘failed back surgery syndrome’ (FBSS). This is a real problem for a condition in which the natural history, even without surgery, is typically of improvement over time. If there is earlier resolution of pain symptoms with surgery versus nonsurgical treatment, but long-term clinical outcome is no different, does this constitute success or failure? FBSS can result as a consequence of poorly executed surgery, but it is much more commonly the result of poor surgical decision-making, inadequate management of patient expectations, or a failure to improve despite a technically sound procedure. A predisposition to develop neuropathic pain may be present in FBSS patients because of genetic or epigenetic factors, independent of surgical technique or patient management, but at present we cannot identify these factors preoperatively, although genetic polymorphisms may eventually help. Patients with more and wider-spread secondary hyperalgesia as well as with psychological dysfunction have a higher risk of poor surgical outcome. Whether this reflects higher susceptibility to establishment of an autonomous centralized state is intriguing to consider, but requires evidence to support it.

Despite some caution about the role of surgery for cLBP, the transformative benefits of surgery in certain clinical scenarios, for example, unrelenting radicular leg pain in patients with concordant nerve root compression on imaging must be recognized. A patient receiving maximum doses of narcotic and neuropathic agents, with significant side effects yet still suffering agonizing pain for many weeks, can be pain-free within hours of surgery. But clearly, this is not always the case, and there are certainly unknown factors that lie beyond sound patient selection.

In summary, the clinical diagnostic and management problem for any individual cLBP patient requires identification of one or several pain states (nociceptive, inflammatory, neuropathic) as well as general pain mechanisms at play. These factors are modified by the individual’s genotype, sex, and psychosocial characteristics, which may individually and collectively influence susceptibility to elevated pain intensity and chronification, as well as therapeutic response and drug metabolism. Current diagnostic tools are too blunt to decipher this complexity, especially under the current pressures (time, financial, documentation, liability) of a busy pain practice. The pain history with self-reported symptoms, even when carefully recorded in detail, is often unreliable. Many aspects of the physical examination suffer from poor validity and reliability or demand extensive time for minute sensory testing with questionable benefit to the patient. Imaging, although important for exclusion of dangerous disease, more often than not does not correlate with the patient’s symptoms and is heavily overutilized without any proven clinical benefit. Diagnostic/therapeutic interventions, like nerve blocks with local anesthetics, remain difficult to interpret and are of controversial clinical benefit.

**Having Recognized the Current Limitations in Chronic Back Pain Diagnosis and Management, How Do We Move Forward?**

**Emerging New Molecular Targets**

Several lines of evidence are providing important new clues about the molecular mechanisms of chronic pain, including human genetic studies that are starting to identify some potentially clinically relevant pain genes. Some of these genes we will briefly highlight, emphasizing therapeutic opportunities.

**Pain Genetics**

A recent twin studies review estimated a heritability of 35% for back and neck pain, highlighting the huge potential for unraveling underlying mechanisms using genetic analysis and for identifying novel targets for pharmacological therapy. Although no adequately powered genome wide study in a large, well-phenotyped cLBP cohort has been carried out so far, several human “pain genes” have been shown to be important in some acquired and familial pain syndromes.

Human genes with a link to dramatic, familial pain phenotypes include SCN9A coding for the voltage-gated sodium channel Na\(_{\text{v}}\)1.7, SCN11A (Na\(_{\text{v}}\)1.9), and TRPA1. Loss-of-function of Na\(_{\text{v}}\)1.7 leads to congenital inability to experience pain without affecting other sensory modalities whereas gain-of-function mutations result in paroxysmal extreme pain disorder and primary erythromelalgia. Less dramatic, but probably more clinically relevant, is the haplotype of a single nucleotide polymorphism which modifies Na\(_{\text{v}}\)1.7 activity and correlates with increased pain scores in several human cohorts suffering from sciatica, osteoarthritis, pancreatitis, lumbar discectomy, scoliosis, fibromyalgia, and carpal tunnel syndrome.
phantom limb pain, and experimental pain.123 Gain of function mutations of SCN11A, coding the nociceptive sodium channel Na1,9, interestingly result in a congenital inability to sense pain in humans99 likely by producing sustained sodium channel inactivation, as can homozygous mutations in PRDM12, an epigenetic regulator that plays a key role in sensory neurogenesis.26 Because of the dramatic phenotype of Na1,7 mutations, with gain and loss of function, as well as the absence of serious cognitive or cardiac effects in individuals with complete loss of function, the channel has spurred huge interest as a drug target. Specific Nav1.7 channels are currently under investigation111 and targeting Na1,7 with an antibody in mouse models of inflammatory and neuropathic pain resulted in significant analgesic effects.94 Clinical trials using selective Na1,7 channel blockers have been successful in conditions like inherited erythromelalgia,190 but so far the limited early trial data have been surprisingly disappointing in other chronic human pain conditions. A gain-of-function mutation in TRPA1, a membrane-associated sensor of environmental irritants, has been identified in a rare disorder called familial episodic pain syndrome, causing upper body pain,39 and several TRPA1 antagonists are currently under investigation in phase I and II clinical trials.

Various haplotypes of other human genes cause less dramatic clinical effects, but might be more clinically relevant because they apply to a much larger population. Examples include: voltage-gated calcium channels CACNG2 (reduced postmastectomy pain116) and CACNA2D3 (reduced postsurgical pain 1 year after discectomy113); voltage-gated potassium channel KCNS1 (increased pain in axial low back pain, amputation, sciatica, phantom limb, and experimental pain in healthy adults180); Na1.8 in patients with painful peripheral neuropathy43; and the cation channel P2X7 (decreased postmastectomy and osteoarthritic pain138). Exploiting these molecular targets remains a challenge because of potentially serious side effects because of their function in many systems.

Besides pain genes altering ion channel properties, genes altering the metabolism of neurotransmitters also seem to account for pain phenotype differences. Examples include genetic variations in catecholamine biosynthesis and transmission (eg, the serotonin transporter gene [SLC6A4] and serotonin and epinephrine receptors162), in the enzymatic breakdown of the neurotransmitters dopamine, epinephrine, and norepinephrine by variations in catecholamine-O-methyltransferase7 and in guanosine triphosphate cyclohydrolase (GCH1), the rate-limiting enzyme for tetrahydrobiopterin (BH4) synthesis, an essential cofactor for phenylalanine, tyrosine, and tryptophan hydroxylases.142 Increased levels of GCH1 and BH4 are implicated in inflammatory and neuropathic pain, whereas blockade of this pathway results in analgesia.92,101 Variants in the human GCH1 haplotype reduce radicular leg pain after discectomy, experimental pain, and improve outcomes after surgically treated degenerative disc disease141. Although the anti-inflammatory drug sulfasalazine, which decreases BH4 levels, has not shown benefit in patients with lumbar spondylarthitis,15 pharmacological blockade of sepiapterin reductase,92 which decreases neuronal and macrophage BH4 production, is effective in rodent chronic inflammatory and neuropathic pain and constitutes a possible pharmacological target for humans.92

**Other New Therapeutic Possibilities**

An interesting target for pharmaceutical intervention is neuroinflammation in the peripheral and CNS, which drives chronic pain via neuron-glial and neuron-immune cell interactions.87 Pharmacological targeting of some of the key molecular players include chemokines (CXCL1, CCL2, and CX3CL1), proteases (MMP9,
cathepsin S, and caspase 6) and the WNT signaling pathway, which have yielded some promising preclinical results, but are compromised by immune suppression and inhibition of synaptic plasticity. One emerging target is leukocyte elastase, released by T cells invading the dorsal root ganglion after peripheral nerve injury, and contributing to neuropathic pain. Sivelestat, a drug currently awaiting U.S. Food and Drug Administration approval and already in clinical use in some countries for treating airway inflammation, inhibits leukocyte elastase and might represent a novel treatment to interrupt immune cell-driven sensitization of DRG neurons.

Other novel drug targets currently undergoing phase II clinical trials on lower back pain are VVZ-149, an antagonist of glycine transporter type 2 and serotonin receptor 2A, for lumbar radiculopathy and epidermal growth factor receptor inhibitors such as cetuximab and panitumumab for various neuropathic pain conditions including complex regional pain syndrome and “failed back syndrome,” as well as ethosuximide, an antiepileptic agent, tenazemub, an anti-NGF antibody, V116517, a TRPV1 inhibitor, cebranopadol, an opioid, and angiotensin type II receptor antagonists.

Restoring spinal cord inhibition using GABA receptor agonists represents another pharmacological strategy, which is mainly challenged by the limited analgesic effect and serious side effects of nonselective GABA receptor agonists like benzodiazepines. However, recent work on different GABA-A receptor subunits has revealed the α2 subunit as a pharmacological target which produces strong antihyperalgesia with reduced sedation, encouraging development of subunit-specific GABA-A receptor benzodiazepines.

Stem cell therapy is another interesting strategy to restore spinal inhibition and thus treat chronic pain conditions, at least experimentally. Delivery of precursors of cortical inhibitory (GABAergic) interneurons results in restoration of GABA-driven inhibition in relevant spinal cord segments to improve neuropathic pain in mice. Intrathecal delivery of bone marrow stromal cells similarly has a therapeutic effect in neuropathic mice models by paracrine secretion of the neuromodulator transforming growth factor-β1 at the site of injured DRG neurons.

Finally, personalized human nociceptor profiling by reprogramming fibroblasts into nociceptors will enable detailed electrophysiological characterization of an individual’s nociceptive phenotype, and could be used to study risk of developing chronic or neuropathic pain and the response profile to particular treatments in a patient. This approach could offer the tantalizing opportunity of one day being able to screen individual patients for pain risk and efficacy in a dish, before initiating treatment.

Conclusions

We have attempted to capture the opportunities and problems facing identification of pain mechanisms in patients, especially those with cLBP. We highlight the limitations of contemporary clinical practice, with an oversimplistic mostly anatomical approach and almost no mechanistic considerations, but recognize that the exciting potential of a more scientific and precision-based strategy will be difficult to achieve. This will require basic scientists and clinicians working together. To do so we need more human-focused efforts by neurobiologists, weeding out, for example, models that are not true surrogates of chronic human pain conditions, and a more scientific focus by clinicians, such that they make a greater attempt to identify where and how their patient’s pain is being generated and use this information to guide treatment choice. We therefore propose the introduction of a pain diagnostic ladder (Fig 2)—analogous to but quite different from the World Health Organization therapeutic ladder—where at each step, one or several mechanisms can be identified that progressively increases the specificity of treatment choice, starting with the broadest category, pain states, and then narrowing down to pain mechanisms, and eventually to molecular targets. Putting such a diagnostic and therapeutic strategy into practice will clearly not be easy, and currently may seem almost impossible, not least because sensitive and precise biomarkers/diagnostic tools of mechanisms are largely absent and because analgesic treatments are generally either not specific for a particular mechanism or there are no treatments available for a definable mechanism. Therefore, until this mechanistic diagnostic approach can evolve and be fully justified scientifically and rigorously validated clinically, chronic pain diagnoses must rely on clinical diagnostic criteria like those described in the AAPT, despite their limitations. Nevertheless, we have a roadmap of what could be possible, and therefore should work together to make it happen.

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