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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.***

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.[51,157,158] Medicine is obviously most impactful when defined

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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 disappointingly poor, 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 discovertebral 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.[34] 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 disability[39,154] 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

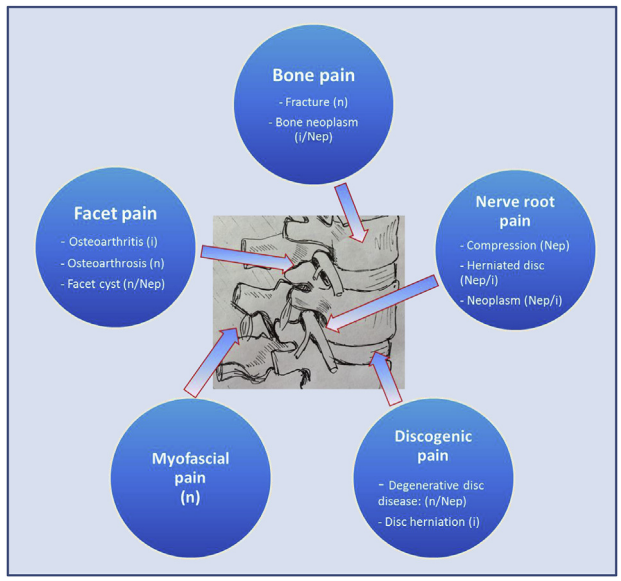

Figure 1. Chronic low back pain drivers. An illustration of pain drivers in chronic low back pain showing their anatomical locus and associated pathology, and the pain states they produce (vertebral column drawing done by Simmie Foster MD, PhD). Abbreviations: i, inflammatory; n, nociceptive; Nep, neuropathic.