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RESEARCH EDUCATION TREATMENT ADVOCACY



Special Article

The ACTTION–APS–AAPM Pain Taxonomy (AAAPT) Multidimensional Approach to Classifying Acute Pain Conditions



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Objective. With the increasing societal awareness of the prevalence and impact of acute pain, there is a need to develop an acute pain classification system that both reflects contemporary mechanistic insights and helps guide future research and treatment. Existing classifications of acute pain conditions are limiting, with a predominant focus on the sensory experience (eg, pain intensity) and pharmacologic consumption. Consequently, there is a need to more broadly characterize and classify the multidimensional experience of acute pain.

Setting. Consensus report following expert panel involving the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION), American Pain Society (APS), and American Academy of Pain Medicine (AAPM).

Methods. As a complement to a taxonomy recently developed for chronic pain, the ACTTION publicprivate partnership with the US Food and Drug Administration, the APS, and the AAPM convened a consensus meeting of experts to develop an acute pain taxonomy using prevailing evidence. Key issues pertaining to the distinct nature of acute pain are presented followed by the agreed-upon taxonomy. The ACTTION-APS-AAPM Acute Pain Taxonomy will include the following dimensions: 1) core criteria, 2) common features, 3) modulating factors, 4) impact/functional consequences, and 5) putative pathophysiologic pain mechanisms. Future efforts will consist of working groups utilizing this taxonomy to develop diagnostic criteria for a comprehensive set of acute pain conditions.

Perspective. The ACTTION-APS-AAPM Acute Pain Taxonomy (AAAPT) is a multidimensional acute pain classification system designed to classify acute pain along the following dimensions: 1) core criteria, 2) common features, 3) modulating factors, 4) impact/functional consequences, and 5) putative pathophysiologic pain mechanisms.

Conclusions. Significant numbers of patients still suffer from significant acute pain, despite the advent of modern multimodal analgesic strategies. Mismanaged acute pain has a broad societal impact as significant numbers of patients may progress to suffer from chronic pain. An acute pain taxonomy provides a much-needed standardization of clinical diagnostic criteria, which benefits clinical care, research, education, and public policy. For the purposes of the present taxonomy, acute pain is considered to last up to seven days, with prolongation to 30 days being common. The current understanding of acute pain mechanisms poorly differentiates between acute and chronic pain and is often insufficient to distinguish among many types of acute pain conditions. Given the usefulness of the AAPT multidimensional framework, the AAAPT undertook a similar approach to organizing various acute pain conditions.

© 2017 The Authors. Published by Elsevier Inc. on behalf of the American Pain Society. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). *Key words:* Acute pain, taxonomy, ACTTION, biopsychosocial, AAAPT, AAPT.

Introduction

n contrast with the pathophysiologic state of chronic pain, acute pain is one of life's inevitable core experiences and has been evolutionarily preserved to serve a critical role in protecting the host against a myriad of threats. Despite this critical role in protecting the host, acute pain can be associated with suffering and a reduction in physical function and productivity—thereby causing a significant burden on the person, their family, and society as a whole. It is now appreciated that acute pain represents a major public health problem.

One of the challenges to both researchers and clinicians is in understanding the distinction between acute and chronic pain. This distinction is important as a better understanding of acute pain may help us to devise therapies to prevent the development of chronic pain. Furthermore, better classification of these pain conditions will help promote more safe, effective, and targeted treatments for individuals suffering from acute pain. Unfortunately, we currently lack precision when discussing the measurement, treatment, research, or even public policy related to acute pain. We therefore need an organized taxonomy of acute pain that establishes a set of common concepts, diagnostic criteria, features, and mechanisms that defines and categorizes the multidimensional aspects of acute pain. This classification will then promote future research into mechanisms, prevention, and treatments for acute pain.

In 2012, an effort to enhance the precision of dialogue about chronic pain was initiated by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) and the American Pain Society (APS). This initiative subsequently developed the ACTTION-APS Pain Taxonomy (AAPT) with the objective of creating an "evidencebased chronic pain taxonomy based on a consistently applied multidimensional framework".¹ Taxonomy in this sense refers to an organization of concepts arranged using hierarchal relationships. The AAPT sought to develop a hierarchical arrangement of characteristics of chronic pain conditions to address the research, clinical, and regulatory limitations of the International Association for the Study of Pain (IASP) taxonomy of pain. AAPT performed this by providing a "standardized, systematic, and evidence-based approach to pain classification that incorporates information regarding biopsychosocial mechanisms and that can be applied to all common chronic pain conditions".²

AAPT developed an approach that included five dimensions that incorporated emerging evidence while retaining some conceptual features of existing chronic pain classifications (Table 1). Further, AAPT proposed specific categories of chronic pain conditions (ie, peripheral and central nervous system; musculoskeletal; orofacial and cranial; visceral, pelvic, and urogenital pain; and disease-associated pains not otherwise specified) that would each be characterized along the five AAPT dimensions by separate working groups.

In 2014, discussions began among APS, ACTTION, and the AAPM about the value of developing a taxonomy of acute pain. Such discussions were spurred by a resurgent interest in acute pain, including increased recognition of the societal burden of the transition from acute to chronic pain, and recognition by a coauthor (DBC) of the unique opportunity for these three organizations to collaborate on such a taxonomy. While a prior working definition of acute pain was formulated by the AAPM Acute Pain Medicine Special Interest Group in 2015 (Table 2), it was apparent that work was needed to further characterize the complex nature of acute pain. A preliminary step in conducting this work was a stateof-the-science expert report that summarized existing literature to inform practice education, research, and health policy.³ The report included an important observation that the organization and integration of acute pain science has been hampered by the lack of a taxonomic structure necessary to promote widespread utilization and acceptance.³ Given the AAPT's previous success in defining a taxonomy of chronic pain, a similar methodology was proposed for the creation of a taxonomy of acute pain: the ACTTION-APS-AAPM Pain Taxonomy (AAAPT) for Acute Pain. The principal objective of the first AAAPT meeting was to review the AAPT taxonomy for chronic pain and determine its appropriateness, applicability, and adaptability if extended to acute pain.

Importance of an Acute Pain Ontology/ Taxonomy

Prevalence of Acute Pain

Despite advances in multimodal analgesia, acute pain remains a pervasive source of suffering. Work by Apfelbaum et al in 2003 demonstrated that 80% of patients suffered acute pain after surgery, and that 86% of these patients reported moderate, severe, or extreme pain.⁴ Moreover, the majority of these patients experienced worse pain following discharge from the hospital. More recent work by Buvanendran in 2015 demonstrated that 66% of patients reported moderate, severe, or extreme pain after surgery and 59% of patients reported moderate, severe, or extreme pain during the first two weeks following hospital discharge.⁵ Within emergency departments, acute pain accounts for up to 78% of visits, with a reported median pain intensity of 8 out of 10 on an 11-point numeric rating scale (NRS).⁶⁻⁹ Finally, primary

Table 1. The ACTTION-APS Chronic Pain Taxonomy (AAPT) Multidimensional Framework

DIMENSION	Description	
1. Core diagnostic criteria	Symptoms, signs, and diagnostic test findings required for the diagnosis of the chronic pain condition. Includes differential diagnosis considerations. ⁶¹	
2. Common features	Additional information regarding the disorder, including common pain characteristics (eg, location, temporal qualities, descriptors), nonpain features (numbness, fatigue), the epidemiology of the condition, and life span considerations, including those specific to pediatric and geriatric populations. These features are important in describing the disorder but are not components of the core diagnostic criteria. ^{61,62}	
3. Common medical and psychiatric comorbidities	Medical and psychiatric disorders that commonly occur with the chronic pain condition. For example, major depression is comorbid with many chronic pain conditions. Also includes chronic overlapping pain conditions, that is, those chronic pain conditions that are comorbid with each other. ⁶³	
4. Neurobiological, psychosocial, and functional consequences		
 Putative neurobiological and psychosocial mechanisms, risk factors, and protective factors 		

This table was reused with permission from Dworkin et al Multidimensional diagnostic criteria for chronic pain: Introduction to the ACTTION–American Pain Society Pain Taxonomy (AAPT). J Pain 2016;17(9 suppl):T1–T9.

482 The Journal of Pain Table 2. AAPM Acute Pain SIG Working Definition of Acute Pain

AAPM APMSIG WORKING DEFINITION: ACUTE PAIN

Acute pain is the physiologic response to and experience of noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviors to avoid potential or actual tissue injury.

care physicians commonly encounter challenging acute pain scenarios (eg, subacute postsurgical pain, acute exacerbations of chronic back pain, acute pharyngitis). In a prospective survey of general practitioners providing acute pain management of ambulatory postsurgical patients, Robaux et al demonstrated a significant need for education and guidelines addressing the diagnosis, optimal treatment, and expected time course for acute pain conditions presenting to the primary care setting.¹⁰

Societal and Clinical Impact

The Institutes of Medicine's (IOM's) report *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research* drew attention to pain as a major health problem and placed it on the national agenda.¹¹ This report called for work to promote tangible objectives to advance pain treatment, education, and research and acknowledged that not all acute pain is being effectively managed. Such efforts are necessary because those with acute pain are currently not offered comprehensive, integrated, evidence-based assessment and treatments.

Acute pain has broader societal impact beyond the initial suffering imparted by the originating insult. Inadequately managed acute pain can lead to patient dissatisfaction, pathophysiologic sequelae, and maladaptive behaviors.¹² With musculoskeletal conditions alone, one in four patients progresses from acute to chronic pain, contributing to serious long-term pain and pain-related physical disability.¹³ The US Department of Health and Human Services National Pain Strategy and the Centers for Disease Control and Prevention (CDC) guidelines on opioid prescriptions for chronic noncancer pain, both recently released, emphasize that chronic pain begins with acute pain.^{14,15} However, the transition from acute to chronic pain remains difficult to predict and little is known about how to prevent its development.¹⁶

Conversely, unintended consequences of the treatment of acute pain can directly threaten patient safety. For example, there exists a wealth of data on the cardiovascular, renal, and gastrointestinal adverse events associated with nonsteroidal anti-inflammatory drugs (NSAIDS), and the risk of hepatic toxicity from over-thecounter analgesics containing acetaminophen remain a substantial public health problem.¹⁷⁻²⁰ Public policy debates on acute pain in the United States have recently centered on opioid analgesics and their effects both on near-term patient safety (eg, respiratory depression, cognitive dysfunction) and longer-term issues of opioid use disorders. It is well known that patients who develop opioid use disorders often have their first exposure to opioids during an acute pain episode.^{21,22} With increasing numbers of surgeries and the push to better control pain, there are concerning trends about increases in both number and dosage of opioid prescriptions following surgery and their contribution to the US opioid epidemic.²³ Researchers have recently identified certain surgeries and patient vulnerabilities that are associated with increased likelihood of being on persistent opioids after surgery.²⁴⁻²⁷ However, much research is needed to determine if preventive strategies can reduce the development of opioid use disorders. An acute pain taxonomy would be an important part of that effort.

Do Any Acute Pain Taxonomies Exist?

The literature on acute pain assessment and treatment largely focuses on acute pain intensity (eg, as assessed by numerical rating scales, verbal rating scales, visual analog scales, various facial scales, or observational pain scales), reflecting a one-dimensional approach to acute pain.²⁸ Such approaches are in keeping with the recommendations of multiple organizations in the 1990s advocating for clinically feasible, standardized approaches to pain assessment, further promulgated by core measures utilized in single-dose analgesic trials.²⁹ Recent studies have expanded such assessments, classifying the acute "pain experience" through a variety of approaches such as multidimensional pain-related patient-reported outcomes and trajectories.³⁰ However, no comprehensive frameworks exist that incorporate mechanistic information in conjunction with pain experience, functional consequences, and psychologic/social impact (ie, biopsychosocial experience) indexed to a standardized array of acute pain conditions. Further, while numerous sources (eg, textbooks, conference proceedings) have provided groupings of acute pain conditions (ie, postsurgical pain, ischemic pain, musculoskeletal pain), such groupings are not unified within a taxonomy.

Impact on Research and Education Initiatives

Not only would the creation of an acute pain taxonomy provide a much-needed standardization of clinical diagnostic criteria, it also would benefit research and education. Numerous documents describe the optimization of acute pain trial designs and call attention to gaps in both the assessment and treatment of acute pain.^{29,31} For example, Gordon et al described a need for future randomized controlled trials (RCTs) and observational studies to include patients with defined phenotypes.³¹ At present, the majority of acute pain studies lack the foundation of a comprehensive acute pain taxonomy to codify inclusion and exclusion criteria and generally do not capture the biopsychosocial outcomes (eq, pain behavior, pain interference, physical function, sleep disturbance, self-efficacy, social satisfaction, etc.) related to acute pain.³² For example, a recent meta-analysis of 15 RCTs addressing acute postmastectomy pain shows a

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predominant focus on pain intensity with little mention of functional or biopsychosocial measures.³³ However, a growing number of investigations are utilizing multidimensional measures to predict postoperative outcomes and embrace such measures to determine analgesic efficacy.³⁴⁻³⁷ Thus, beyond establishing a framework for inclusion and exclusion criteria, an evidence-based acute pain taxonomy offers the potential to illuminate the complex biopsychosocial experience of acute pain and encourage research to move beyond unidimensional measures of pain intensity.

Importantly, a multidimensional approach to an acute pain taxonomy would also provide an essential foundation for training acute pain medicine physicians. In 2014, the Accreditation Council for Graduate Medical Education (ACGME) Board of Directors voted to accept Regional Anesthesia and Acute Pain Medicine as an accredited fellowship, a move that was later approved in October 2016. Since that time, significant effort has led to the creation of a set of competencies embracing the comprehensive practice of acute pain medicine. An evidence-based acute pain taxonomy will advance the structure and content of this curriculum. Moreover, this structure will support ongoing efforts to bolster pain education across medical specialties and ancillary services.

Acute Pain Taxonomy Considerations: Differentiating Acute from Chronic?

The AAAPT Steering Committee convened a meeting of experts in April of 2016 with the goal of addressing the need for a comprehensive acute pain taxonomy. This two-day conference began with discussions on 1) the need for formal taxonomies for pain and 2) whether initial efforts in developing a taxonomy for chronic pain by the AAPT could serve as a basis for developing an acute pain taxonomy. Presentations on the historical contexts of acute pain through both ancient and modern history segued into a review of known biological mechanisms of acute pain (Table 3). Discussions then turned to principles of taxonomic organization and the validity

Table 3. Presentation Topics During AAAPT Taxonomy Development Meeting

Presented Topics

AAPT chronic pain effort (RF/RD) Distinctions among acute, subacute, and chronic pain (DC) Pathophysiologic mechanisms and acute pain conditions (TB) Taxonomy of acute pain conditions (PT) Acute surgical/procedural pain (CW) Acute trauma pain (CB) Acute musculoskeletal pain (SS) Acute visceral pain (MK) Cancer/immune mediated acute pain (KT) Acute neuropathic pain (SR) Acute orofacial pain (PD) Acute pain in pediatric, geriatric, and special populations (SW) Approached to providing an evidence base for acute pain diagnostic criteria (SB) and reliability of diagnostic criteria as a means of informing further development. Following discussions focused on specific types of acute pain including postoperative pain, acute pain related to trauma and burn, visceral pain, acute cancer pain, acute neuropathic pain, acute musculoskeletal pain, acute orofacial pain, and acute pain in special populations such as pediatrics. These discussions culminated in a group discussion on developing a multidimensional structure for acute pain taxonomy based on the AAPT chronic pain initiative.

Time-Based Criteria

In the AAAPT discussions, differentiation of acute pain from chronic pain quickly emerged as a principal topic, with an emphasis on timing as a key differentiator. Historically, the Food and Drug Administration has suggested that pain occurring within 30 days of an insult or injury is considered acute pain and that after 90 days postinjury/-insult such pain is referred to as chronic pain.^{32,38} Recent CDC guidelines pertaining to opioid prescriptions posit a 72-hour period for acute pain treatment of nontraumatic and nonsurgical origins.¹⁴ Other experts have variously characterized durations of acute pain ranging from seven to 14 days, with numerous examples throughout the perioperative, emergency department, and primary care settings. The heterogeneity of definitions of acute pain with respect to delineations of time intervals, as well as clinical contexts and excluded patient populations, highlights the gaps and opportunities raised with most of the a priori time thresholds.

In the search for a definitive cut-point between acute and chronic pain, it is important to consider the perspective that acute and chronic pain are not entirely "separate" entities, but rather different aspects along a continuum of pain.³⁹ This continuum may extend beyond established characteristics of intensity and timing; for instance, contexts such as initial pain intensity ratings may influence the segue between acute and chronic.⁴⁰ Given the perspective of a continuum from acute to chronic pain, a clear separation of acute from chronic pain may be impossible, and a focus on "at what time" acute pain becomes chronic may be misguided or misleading and unnecessary. At present, the vague and ill-defined term "subacute" pain has been used to define this time period where acute pain may or may not become chronic pain. Unique attributes of pain during this period, however, have been described. For example, in a study of 96 patients undergoing total knee arthroplasty, more patients described neuropathic pain symptoms at six weeks postoperatively when compared with the immediate postoperative setting or at later time points greater than six months.⁴¹ At this time, the term "subacute" is used only descriptively until this period can be more precisely characterized mechanistically and phenomenologically.

Our evolutionary approach thus follows that of the AAPT effort on chronic pain; we simply do not have sufficient mechanistic data at this time to render a "revolutionary" consideration of the acute to chronic transition.

Given numerous examples of prolonged and/or repetitive nociception/pain events that do not progress into chronic pain, future iterations of the AAAPT taxonomy may be able to better focus on the "why" and "how" for the transition between acute and chronic pain rather than solely its temporal parameters.

Despite concerns regarding a formal cutoff point for acute pain, AAAPT adopted the following time-based definition of acute pain for pragmatic and heuristic purposes at this time:

Acute pain is considered to last up to seven days, with the following qualifications:

- 1. Its duration reflects the mechanism and severity of the underlying inciting event.
- 2. Prolongations from seven to 30 days are common.
- 3. Prolongations beyond the duration of acute pain but not extending past 90 days postonset/-injury are common. This refers to the ill-defined but important period of "subacute" pain that warrants further specification and consideration in future taxonomic, research, and regulatory efforts.
- Our understanding of pain mechanisms is currently insufficient to link these durations to specific physiologic mechanisms.

Unique Attributes of Acute Pain

Apart from the temporal differentiation separating acute and chronic pain, there are other characteristics that differentiate the two conditions. One of the foremost differences between acute and chronic pain remains the ambiguity of its contextual meaning. Acute pain has often been considered a protective mechanism against further injury that may facilitate recovery from injury. Those aspects of acute pain that are normative, protective, and helpful deserve special attention as they contrast starkly with chronic pain, which is invariably considered pathologic with no direct benefit to the patient. Such contrasts are not unique to acute and chronic pain. For instance, immune function and inflammation are generally considered normative, protective responses against insults yet can generate pathologic states that are life-threatening (eg, sepsis, autoimmune disease).^{42,43} Notably, as with allergy, inflammation, anaphylaxis, and sepsis, the transition points seem key, yet the nature of the points of inflection remains enigmatic.

Mechanism-Based

Similar to the AAPT chronic pain experience, it was hoped that the AAAPT could inform its dimensional constructs by mapping onto underlying pain mechanisms. As with chronic pain, it was agreed that the current understanding of acute pain mechanisms poorly differentiates between acute and chronic pain and is often insufficient to distinguish among many types of acute pain conditions. One of the foremost examples of such a failure is the intertwined nature of the pathophysiologic mechanisms (eg, nociceptive, neuropathic, inflammatory, ischemic) contributing to acute pain. As each of these components is present in nearly all acute pain conditions, distinguishing among acute pain conditions according to their nociceptive, neuropathic, or inflammatory components is presently infeasible. A similar issue arises in considering biochemical mediators as current evidence suggests that acute and chronic disease states often display similar profiles of peripheral mediators.

Another approach to differentiate between acute and chronic pain, or among acute pain types, is to consider whether the mechanism of sensitization is peripheral or central. Although acute pain may initially involve prominent peripheral sensitization, it may also occur during chronic pain and therefore discourages reliance on the criterion of peripheral sensitization as a key differentiator between acute and chronic pain. On the other hand, central sensitization seems to play a larger role (and has been characterized more extensively) in chronic pain conditions but yet is evident in acute pain as well. Future research will be needed to better characterize the relative contributions of peripheral and central sensitization to the overall acute pain process—and its transition to chronic pain.

The presence and nature of tissue injury probably differentiates best between acute and chronic pain, as well as among different types of acute pain conditions. At the level of tissue injury, distinct profiles of injured structures, tissue-specific mediators, receptors, and responses may help differentiate acute pain conditions. For instance, the high affinity receptor (trkA) for the nociceptive mediator nerve growth factor (NGF) is expressed in notably higher levels in visceral bladder afferent vs cutaneous sensory afferents.⁴⁴ Further, acute pain stemming from periosteal injury has distinct mechanisms, mediators, and transmission compared with acute pain stemming from cutaneous injury. While many examples of acute tissue injury involve damage to an array of tissues (post-traumatic or postsurgical models), other etiologies are more tissue specific. For example, acute neuropathic pain may be in part initiated by infectious and inflammatory injury, more specifically to neural structures such as dorsal root ganglion neurons. Similarly, certain types of acute pain are strongly associated with a particular anatomic location, for example, fracture or burn pain.

Dimensional Considerations

Given the usefulness of the AAPT multidimensional framework, the AAAPT undertook a similar approach to organizing various acute pain conditions. In the consensus approach that emerged from the AAAPT discussions, acute pain and chronic pain are considered subclasses of pain. Acute pain conditions are broadly characterized according to the five dimensions that are described below. Specific categories of prototypical acute pain conditions would be differentiated according to these five dimensions. Notably in this construct, each dimension can be further organized as needed during future iterations. A strategic decision was made to defer discussions on acute pain assessment and treatment for a future effort.

Kent et al Table 4. AAAPT Acute Pain Dimensions

Dimension 1: Core criteria	Specifies the inciting event, timing from the event, and tissue involved. Inciting events descriptions include ICD10x diagnostic and/or procedure codes where possible.	
Dimension 2: Common features	Characterizes the acute pain condition through common pain variables (symptoms, signs, quality). Emphasizes temporal trajectory, physical spatial distribution, and recovery expectations.	
Dimension 3: Modulating factors	Includes comorbidities (ie, opioid tolerance) as well as sociodemographic, biopsychosocial, and surgical factors that may modulate the acute pain experience. Biopsychosocial risk factors (eg, catastrophizing) for significant acute pain are considered here.	
Dimension 4: Impact/functional consequences	Describes the recovery trajectory including the interrelations of physical, social, psychologic, and vocational consequences resulting from the acute pain condition.	
Dimension 5: Putative mechanisms	Includes the neurobiological mechanisms related to the acute pain condition. Considers all phases of the acute pain experience and identifies risk factors for development of significant acute pain. Addresses genetic- and mechanism-based processes to guide treatment.	

Dimensions

Discussion on how to categorize acute pain conditions began with the five dimensions used for the AAPT. These were extended to consider 10 to 12 dimensions, before then collapsing back to a final five dimensions aligned with, but differing from, the AAPT chronic pain dimensional framework. The rationale for this approach included recognition of the close link between acute and chronic pain and the potential benefits of aligning their dimensional structures for research and practice updates. The AAAPT specified that no one dimension be considered more important than or superior to the others. The five dimensions for the AAAPT were finalized as 1) core criteria, 2) common features, 3) modulating factors, 4) impact/functional consequences, and 5) putative pathophysiologic pain mechanisms (Table 4).

Dimension 1: Core Criteria

The core criteria represent the key features of a given acute pain condition that permit it to be diagnosed and distinguished from other acute pain conditions. Unlike the AAPT dimension 1 for chronic pain, which emphasizes the clinical features of the pain condition itself, the core criteria here put greater emphasis on the nature of the inciting event. This is because, in many cases, distinct acute pain conditions may not differ so much in their characteristic signs and symptoms, but rather, in their inciting event, a feature not always identifiable in chronic pain. Moreover, the inciting event would often be associated with a specific International Classification of Disease Version 10 (ICD10x) diagnostic or procedure code that in turn would link the acute pain taxonomy to established diagnostic and procedural ontologies. The international standardization of the ICD system links this dimension to a broader array of efforts to codify various classification systems used throughout health care. This feature also permits the AAAPT taxonomy to align with existing clinical entities. Further, this approach enables a mechanism to remap the existing dimensional framework to future disease classification schemas according to the prescribed approaches normally specified during such ICD transitions.

Another key aspect of dimension 1 is the time elapsed from the inciting event to the observation of the patient, which is critical for defining the condition as "acute." If not specified, the time from the inciting event within this framework is presumed to follow the proposed time-based criteria for acute pain described above.

The core criteria are intended to be the defining aspects of each condition. They differ from dimension 2: common features, in that the latter is intended to be a more comprehensive and descriptive collection of characteristics of each acute pain condition that are not necessary for a diagnosis.

Dimension 2: Common Features

Attributes of this dimension include common painrelated signs, symptoms, and qualities of each acute pain condition. Special emphasis was placed on three additional attributes in this category: temporal trajectory, spatial and anatomical distribution, and anticipated recovery. Current and anticipated temporal trajectories (ie, characteristic changes in a given pain measure over time in the acute phase) are key elements given their impact on both treatment and the acute-to-chronic transition. Likewise, spatial and anatomical distribution is intended to reflect not only radiation but also peripheral, and potentially central, sensitization. Anticipated recovery refers to the expected duration of recovery, but could also be considered a binary response. For example, patients suffering from an uncomplicated ankle sprain will substantially recover pre-injury function, while patients suffering from hemipelvectomy for sarcoma will likely suffer from persistent pain and loss of functioning stemming in part from this pain. Although it is a specific attribute distinct from other features, anticipated recovery is frequently impacted by core criteria (dimension 1), modulating factors (dimension 3), impact/functional consequences (dimension 4), and putative pain pathophysiologic mechanisms (dimension 5).

Dimension 3: Modulating Factors

Modulating factors include not only comorbid medical conditions, but also sociodemographic, biological, clinical, behavioral, and affective conditions likely to modulate the acute pain experience (eg, pain catastrophizing, state anxiety, opioid tolerance, evidence of central sensitization, adverse childhood experiences).^{35,36,45-47} These factors may include factors pertaining to spatiotemporal summation and diffuse

noxious inhibitory control, which more recently has been termed conditioned pain modulation to specify "psychosocial paradigms in which a conditioning stimulus is used to affect a test stimulus".48-51 Dimension 3 strongly considers the context of the inciting event. This context includes not just the events surrounding the inciting event of dimension 1, but also the social setting in which the patient lives and works. Such environmental factors may extend to the treatment environment and clinicians that may influence which diagnostic and therapeutic interventions are offered. For example, following a significant acute pain event, availability of analgesic modalities/techniques is highly dependent on the environment of care (clinic, rural hospital, large tertiary care center). Previous pain experiences may be included here. Finally, a variety of neurobiological mechanisms may also modulate the acute pain experience. While far from condition specific, such mechanisms may serve as risk factors for significant acute pain by either impacting pain sensitivity (eq, genetic variants of COMT, TRPA1) or influencing treatment options such as in drug metabolism/ receptor interaction (eg, genetic variants of CYP2D6, OPRM1).52-56

Dimension 4: Impact/Functional Consequences

The fourth dimension describes the recovery trajectory including the interrelations of physical, social, psychologic, and vocational consequences resulting from the acute pain condition. This dimension highlights that in acute pain syndromes the acute pain itself may not be the principal factor requiring attention, but rather an important hurdle to recovery from the principal diagnosis/procedure. For example, patients undergoing total hip arthroplasty reporting severe pain also report significant disturbances in social relations and mood.⁵⁷ Operationally, the National Pain Strategy has taken the step of defining "high-impact chronic pain" as "being associated with substantial restriction of participation in work, social, and self-care activities for six months or more." Similar definitions could also be applied to "high-impact acute pain."

Dimension 5: Putative Pain Pathophysiologic Mechanisms

When possible, this dimension characterizes painrelevant neurobiologic pathways prior to, during, and after the inciting event. This dimension delineates the step-by-step natural history of nociceptive, neuropathic, and inflammatory processes that occur at the site of injury, extending through cerebral processing. One example would be activation of visceral nociceptive afferents (eg, TRPV1 activation in urothelial cells) that transmit noxious stimuli via autonomic ganglia through a variety of spinal pathways (eg, spinohypothalamic) ultimately processed in cerebral locations such as the anterior cingulate gyrus.⁵⁸⁻⁶⁰ While we lack the knowledge to classify acute pain conditions on a purely mechanistic basis and many overlapping mediators exist, such condition-specific descriptions provide a platform for future research and clarification. Further, while the exact processes underlying the transition from acute to chronic pain remain nebulous, initial iterations of this taxonomy will consider descriptions of such postulated mechanisms (eg, peripheral/central sensitization) for at-risk acute pain conditions (eg, amputation, thoracotomy, polytrauma).

Acute Pain Categories

Organization of specific prototypical acute pain conditions diverged from the AAPT model in allowing two broad categories, within which particular conditions would be placed (Table 5). The first category specifically considers acute pain related to surgery, including procedural pain. Within this category fall acute pain conditions related to different types of surgery, such that acute pain from appendectomy could be differentiated from acute pain from thoracotomy, knee replacement, or cesarean delivery. For current purposes, we use the term "procedural pain" to refer to acute pain that exists during the time of a procedure itself, implying the expectation of minimal to no postprocedural discomfort. Examples of this might include percutaneous insertion of an intravenous catheter, endoscopy, cardiac catheterization, or extracorporeal shock wave lithotripsy.

One critical rationale for this differentiation between surgical and nonsurgical categories of acute pain pertains to the timing, anticipation, and possible preventive aspects of scheduled tissue injury. Importantly, this scheduling permits the opportunity to intervene prior to the onset of and during tissue injury and to prospectively plan for analgesia and functional recovery in the time immediately following injury. From a mechanistic standpoint, intervention to decrease acute pain

Table 5. Acute Pain Categories to be Defined Under Dimensional Structure in Future Working Groups

Acute Pain Categories		
Surgical/Procedural	Nonsurgical	
Cardiovascular surgery Dental surgery General surgery Neurosurgery Obstetric/gynecologic surgery Ophthalmic surgery Orthopedic surgery Otolaryngology Out of operating room procedures Pediatric surgery Plastic and reconstructive surgery Thoracic surgery Transplant surgery Urology	Acute neuropathic (eg, radiculopathy) Acute ischemic (eg, myocardial ischemia) Visceral (eg, renal colic) Trauma (including burns) Orofacial Musculoskeletal Special populations Adolescent Cancer Elderly Labor Pediatric/neonatal/fetal Sickle Cell Other	

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in the perioperative/periprocedural period may be key in the effort to block the transition to chronic pain. However, further specification will be necessary to address the role of tissue injury and pain that predates the surgery itself.

The second category comprises acute pain related to nonsurgical etiologies. This is a large category, and thus subcategories of nonsurgical pain include trauma (including burn), visceral, ischemic, orofacial, acute neuropathic, and musculoskeletal, as manifested in the population at large or in special populations (labor, sickle cell, pediatrics, etc.). Similar to the aforementioned chronic pain taxonomy, this approach is admittedly imperfect as many of the above acute pain conditions share overlapping characteristics with surgical acute pain (ie, traumatic laceration vs surgical incision).

Two important nonsurgical categories, visceral and ischemic pain, illustrate this overlap. Numerous surgical interventions contain these pain types as subcomponents. For example, surgical bowel intervention often leads to acute visceral pain. Additionally, conditions such as spontaneous and traumatic limb or abdominal compartment syndrome, while largely ischemic in nature, are often surgically related. Commentary on such mechanisms will certainly be required in the future working groups addressing surgical subtypes. However, given the significant number of discrete acute visceral (eg, renal colic) and ischemic (eg, myocardial ischemia)

References

1. Fillingim RB, Bruehl S, Dworkin RH, et al: The ACTTION-American Pain Society Pain Taxonomy (AAPT): An evidence-based and multidimensional approach to classifying chronic pain conditions. J Pain 15:241-249, 2014

2. Merskey H, Bogduk N: Classification of Chronic Pain. Seattle, International Association for the Study of Pain, IASP PRESS, 1994, p 1

3. Tighe P, Buckenmaier CC, Boezaart AP, et al: Acute pain medicine in the United States: A status report. Pain Med 16:1806-1826, 2015

4. Apfelbaum JL, Chen C, Mehta SS, Gan TJ: Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 97:534-540, 2003

5. Buvanendran A, Fiala J, Patel KA, et al: The incidence and severity of postoperative pain following inpatient surgery. Pain Med 16:2277-2283, 2015

6. Tanabe P, Buschmann M: A prospective study of ED pain management practices and the patient's perspective. J Emerg Nurs 25:171-177, 1999

7. Johnston CC, Gagnon AJ, Fullerton L, et al: One-week survey of pain intensity on admission to and discharge from the emergency department: A pilot study. J Emerg Med 16: 377-382, 1998

8. Todd KH, Ducharme J, Choinière M, et al: Pain in the emergency department: Results of the Pain and Emergency Medicine Initiative (PEMI) multicenter study. J Pain 8: 460-466, 2007

conditions that are not necessarily surgical in nature, these were considered appropriate initial components of the nonsurgical categories. Indeed, the context, environment, and psychosocial modulating factors may account for greater individual variability of the pain experience than currently available mechanistic characterization of such overlapping conditions.

Further development of the description and taxonomy of all specific acute pain subcategories will be carried out by several ongoing AAAPT workgroups. Each acute pain condition will be described according to the five AAAPT dimensions, with additional characterization as needed.

Conclusion

This multidimensional framework proposed by the AAAPT provides a taxonomy of acute pain that will allow the various acute pain conditions to be characterized in a uniform fashion. This acute pain taxonomy is intended to be a dynamic framework that may continually evolve alongside ever-emerging evidence on the nature and impact of acute pain. While separate from the AAPT taxonomy of chronic pain conditions, the long-term vision is to establish sufficient understanding of pain such that a standard, unifying model can evolve, linking the proposed dimensions of both the acute and chronic pain taxonomies.

9. Cordell WH, Keene KK, Giles BK, et al: The high prevalence of pain in emergency medical care. Am J Emerg Med 20:165-169, 2002

10. Robaux S, Bouaziz H, Cornet C, et al: Acute postoperative pain management at home after ambulatory surgery: A French pilot survey of general practitioners' views. Anesth Analg 95:1258-1262, **2002**

11. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education: Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC, National Academies Press, 2011

12. Sinatra R: Causes and consequences of inadequate management of acute pain. Pain Med 11:1859-1871, 2010

13. Walsh NE, Brooks P, Hazes JM, et al: Standards of care for acute and chronic musculoskeletal pain: The bone and joint decade (2000–2010). Arch Phys Med Rehabil 89:1830-1845, 2008

14. Dowell D, Haegerich TM, Chou R: CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep 65:1-49, 2016

15. Interagency Pain Research Coordinating Committee: National pain strategy. Available at: https://iprcc.nih.gov/ National_Pain_Strategy/NPS_Main.htm; 2015, Accessed December 2016

16. Katz J, Seltzer Z: Transition from acute to chronic postsurgical pain: Risk factors and protective factors. Expert Rev Neurother 9:723-744, **2009**

17. Salvo F, Fourrier-Réglat A, Bazin F, et al: Cardiovascular and gastrointestinal safety of NSAIDs: A systematic review of meta-analyses of randomized clinical trials. Clin Pharmacol Ther 89:855-866, **2011**

18. Scheiman JM: NSAID-induced gastrointestinal injury: A focused update for clinicians. J Clin Gastroenterol 50:5-10, 2016

19. Ng SC, Chan FKL: NSAID-induced gastrointestinal and cardiovascular injury. Curr Opin Gastroenterol 26:611-617, 2010

20. Mathiesen O, Wetterslev J, Kontinen VK, et al: Adverse effects of perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: A topical review. Acta Anaesthesiol Scand 58:1182-1198, **2014**

21. Calcaterra SL, Yamashita TE, Min S-J, et al: Opioid prescribing at hospital discharge contributes to chronic opioid use. J Gen Intern Med 31:478-485, **2016**

22. Wasan AD, Correll DJ, Kissin I, O'Shea S, Jamison RN: latrogenic addiction in patients treated for acute or subacute pain: A systematic review. J Opioid Manag 2:16-22, 2006

23. Wunsch H, Wijeysundera DN, Passarella MA, Neuman MD: Opioids prescribed after low-risk surgical procedures in the United States, 2004–2012. JAMA 315: 1654-1657, 2016

24. Sun EC, Darnall BD, Baker LC, Mackey S: Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. JAMA Intern Med 176: 1286-1293, 2016

25. Hah JM, Sharifzadeh Y, Wang BM, et al: Factors associated with opioid use in a cohort of patients presenting for surgery. Pain Res Treat 2015:829696-829698, 2015

26. Hah JM, Mackey S, Barelka PL, et al: Self-loathing aspects of depression reduce postoperative opioid cessation rate. Pain Med 15:954-964, 2014

27. Carroll I, Barelka P, Wang CKM, et al: A pilot cohort study of the determinants of longitudinal opioid use after surgery. Anesth Analg 115:694, 2012

28. Hjermstad MJ, Fayers PM, Haugen DF, et al: Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. J Pain Symptom Manage 41:1073-1093, 2011

29. Cooper SA, Desjardins PJ, Turk DC, et al: Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. Pain 157:288-301, 2016

30. Chapman CR, Donaldson GW, Davis JJ, Bradshaw DH: Improving individual measurement of postoperative pain: The pain trajectory. J Pain 12:257-262, **2011**

31. Gordon DB, de Leon-Casasola OA, Wu CL, et al: Research gaps in practice guidelines for acute postoperative pain management in adults: Findings from a review of the evidence for an American Pain Society clinical practice guideline. J Pain 17:158-166, **2016**

32. Administration UFAD: Guidance for industry analgesic indications: Developing drug and biological products. Available at: http://www.fda.gov/downloads/drugs/guidance complianceregulatoryinformation/guidances/ucm384691.pdf; 2014, Accessed December 2016

33. Schnabel A, Reichl SU, Kranke P, Pogatzki-Zahn EM, Zahn PK: Efficacy and safety of paravertebral blocks in breast surgery: A meta-analysis of randomized controlled trials. Br J Anaesth 105:842-852, 2010

34. Ilfeld BM, Madison SJ, Suresh PJ, et al: Persistent postmastectomy pain and pain-related physical and emotional functioning with and without a continuous paravertebral nerve block: A prospective 1-year follow-up assessment of a randomized, triple-masked, placebo-controlled study. Ann Surg Oncol 22:2017-2025, 2015

35. Brummett CM, Janda AM, Schueller CM, et al: Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplastya prospective, observational cohort study. Anesthesiology 119:1434-1443, **2013**

36. Janda AM, As-Sanie S, Rajala B, et al: Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. Anesthesiology 122:1103-1111, **2015**

37. Goesling J, Moser SE, Zaidi B, et al: Trends and predictors of opioid use after total knee and total hip arthroplasty. Pain 157:1259-1265, **2016**

38. Dworkin RH, Turk DC, Basch E, et al: Considerations for extrapolating evidence of acute and chronic pain analgesic efficacy. Pain 152:1705-1708, 2011

39. Carr DB, Goudas LC: Acute pain. Lancet 353:2051-2058, 1999

40. Thyregod HG, Rowbotham MC, Peters M, et al: Natural history of pain following herpes zoster. Pain 128:148-156, 2007

41. Phillips JRA, Hopwood B, Arthur C, Stroud R, Toms AD: The natural history of pain and neuropathic pain after knee replacement: A prospective cohort study of the point prevalence of pain and neuropathic pain to a minimum three-year follow-up. Bone Joint J 96–B: 1227-1233, **2014**

42. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315:801-810, 2016

43. Sakkas Ll, Bogdanos DP: Infections as a cause of autoimmune rheumatic diseases. Auto Immun Highlights 7:13, 2016

44. Bennett DL, Dmietrieva N, Priestley JV, Clary D, McMahon SB: trkA, CGRP and IB4 expression in retrogradely labelled cutaneous and visceral primary sensory neurones in the rat. Neurosci Lett 206:33-36, 1996

45. Keltner JR, Furst A, Fan C, et al: Isolating the modulatory effect of expectation on pain transmission: A functional magnetic resonance imaging study. J Neurosci 26: 4437-4443, 2006

46. Fields HL: Pain modulation: Expectation, opioid analgesia and virtual pain. Prog Brain Res 122:245-253, **2000**

47. Schreiber KL, Martel MO, Shnol H, et al: Persistent pain in postmastectomy patients: Comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. Pain 154: 660-668, 2013

48. Yarnitsky D: Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): Its relevance for acute and chronic pain states. Curr Opin Anaesthesiol 23: 611-615, **2010**

49. van Wijk G, Veldhuijzen DS: Perspective on diffuse noxious inhibitory controls as a model of endogenous pain modulation in clinical pain syndromes. J Pain 11:408-419, 2010

50. Nielsen J, Arendt-Nielsen L: Spatial summation of heat induced pain within and between dermatomes. Somatosens Mot Res 14:119-125, 1997

Kent et al

51. Arendt-Nielsen L, Graven-Nielsen T, Svensson P, Jensen TS: Temporal summation in muscles and referred pain areas: An experimental human study. Muscle Nerve 20:1311-1313, 1997

52. Smith MT, Muralidharan A: Pharmacogenetics of pain and analgesia. Clin Genet 82:321-330, 2012

53. Nackley AG, Tan KS, Fecho K, et al: Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both β 2- and β 3-adrenergic receptors. Pain 128: 199-208, 2007

54. Crist RC, Berrettini WH: Pharmacogenetics of OPRM1. Pharmacol Biochem Behav 123:25-33, 2014

55. Yang Z, Yang Z, Yang Z, et al: CYP2D6 poor metabolizer genotype and smoking predict severe postoperative pain in female patients on arrival to the recovery room. Pain Med 13:604-609, **2012**

56. Somogyi AA, Barratt DT, Coller JK: Pharmacogenetics of opioids. Clin Pharmacol Ther 81:429-444, 2007

57. Dihle A, Helseth S, Paul SM, Miaskowski C: The exploration of the establishment of cutpoints to categorize the severity of acute postoperative pain. Clin J Pain 22: 617-624, 2006

58. Cervero F, Laird JMA: Understanding the signaling and transmission of visceral nociceptive events. J Neurobiol 61: 45-54, 2004

59. Cervero F, Laird JM: Visceral pain. The Lancet 353: 2145-2148, 1999

60. Sikandar S, Dickenson AH: Visceral pain: The ins and outs, the ups and downs. Curr Opin Support Palliat Care 6: 17-26, **2012**

61. Fillingim RB, Loeser JD, Baron R, Edwards RR: Assessment of Chronic Pain: Domains, Methods, and Mechanisms. J Pain 17(9 Suppl):T10-T20, **2016**

62. Walco GA, Krane EJ, Schmader KE, Weiner DK: Applying a Lifespan Developmental Perspective to Chronic Pain: Pediatrics to Geriatrics. J Pain 17(9 Suppl):T108-T117, 2016

63. Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD: Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification. J Pain 17(9 Suppl): T93-T107, 2016

64. Turk DC, Fillingim RB, Ohrbach R, Patel KV: Assessment of Psychosocial and Functional Impact of Chronic Pain. J Pain 17(9 Suppl):T21-T49, 2016

65. Vardeh D, Mannion RJ, Woolf CJ: Toward a Mechanism-Based Approach to Pain Diagnosis. J Pain 17(9 Suppl): T50-T69, 2016

66. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD: The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. J Pain 17(9 Suppl):T70-T92, 2016