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AAPT Diagnostic Criteria for Chronic Cancer Pain Conditions

Judith A. Paice, PhD, RN, Matt Mulvey, PhD, Michael Bennett, MD, Patrick M. Dougherty, PhD, John T. Farrar, MD, PhD, Patrick W. Mantyh, PhD, Christine Miaskowski, RN, PhD, Brian Schmidt, DDS, MD, PhD, Thomas J. Smith, MD

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AAPT Diagnostic Criteria for Chronic Cancer Pain Conditions

Judith A. Paice, PhD, RN
Division of Hematology-Oncology
Northwestern University, Feinberg School of Medicine
Chicago, IL

Matt Mulvey, PhD
Academic Unit of Palliative Care
Leeds Institute of Health Sciences
University of Leeds
Leeds, UK

Michael Bennett, MD
Academic Unit of Palliative Care
Leeds Institute of Health Sciences
University of Leeds
Leeds, UK

Patrick M. Dougherty, PhD
The Division of Anesthesia and Critical Care Medicine
The University of Texas M.D. Anderson Cancer Center
Houston, TX

John T. Farrar, MD, PhD
Department of Epidemiology, Neurology, and Anesthesia
University of Pennsylvania
Philadelphia, PA

Patrick W. Mantyh, PhD
Department of Pharmacology
University of Arizona
Tucson, AZ

Christine Miaskowski, RN, PhD
Department of Physiological Nursing
University of California
San Francisco, CA

Brian Schmidt, DDS, MD, PhD
Bluestone Center for Clinical Research
New York University College of Dentistry
New York, NY

Thomas J. Smith, MD
Department of Oncology
The Johns Hopkins Hospital

Baltimore, MD

Corresponding Author:
Judith A. Paice, PhD, RN
Director, Cancer Pain Program
Division of Hematology-Oncology
676 N. St. Clair Street, Suite 850
Chicago, IL 60611
312-695-4157
312-695-6189 fax
j-paice@northwestern.edu

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Abstract

Chronic cancer pain is a serious complication of malignancy or its treatment. Currently, no comprehensive, universally accepted cancer pain classification system exists. Clarity in classification of common cancer pain syndromes would improve clinical assessment and management. Moreover, an evidence-based taxonomy would enhance cancer pain research efforts by providing consistent diagnostic criteria, ensuring comparability across clinical trials. As part of a collaborative effort between the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) and the American Pain Society (APS), the ACTTION-APS Pain Taxonomy (AAPT) initiative worked to develop the characteristics of an optimal diagnostic system.[59, 65] Following the establishment of these characteristics, a working group consisting of clinicians and clinical and basic scientists with expertise in cancer and cancer-related pain was convened to generate core diagnostic criteria for an illustrative sample of 3 chronic pain syndromes associated with cancer (i.e., bone pain and pancreatic cancer pain as models of pain related to a tumor) or its treatment (i.e., chemotherapy-induced peripheral neuropathy). A systematic review and synthesis was conducted to provide evidence for the dimensions that comprise this cancer pain taxonomy. Future efforts will subject these diagnostic categories and criteria to systematic empirical evaluation of their feasibility, reliability and validity and extension to other cancer-related pain syndromes.

Perspective

The ACTTION-APS chronic cancer pain taxonomy provides an evidence-based classification for 3 prevalent syndromes, namely malignant bone pain, pancreatic cancer pain, and chemotherapy-induced peripheral neuropathy. This taxonomy provides consistent diagnostic criteria, common features, co-morbidities, consequences, and putative

mechanisms for these potentially serious cancer pain conditions that can be extended and applied with other cancer-related pain syndromes.

Key words

Cancer pain, taxonomy, bone pain, chemotherapy-induced peripheral neuropathy, pancreatic cancer

AAPT Diagnostic Criteria for Chronic Cancer Pain Conditions

Introduction

One significant barrier to better understanding the growing dilemma of chronic cancer pain is the lack of consistent diagnostic criteria that can be used in research and clinical settings. A common taxonomy would provide a foundation for studies of the prevalence, as well as the consequences of these pain syndromes for people with cancer; present evidence for the significance of this problem; support the need for improvements in management; and increase research efforts.[153] This standardized classification system would enhance research efforts by ensuring greater homogeneity in pain conditions across clinical trials and support the development of animal models to replicate these cancer pain conditions. Ultimately, valid and reliable diagnostic criteria would facilitate clinical assessment and management and potentially guide prognostic accuracy.[59, 65]

Current systems to classify cancer pain provide general clinical utility. Cancer pain is often organized by its intensity (e.g., mild, moderate or severe), its expected time course (e.g., acute versus chronic), its presumed underlying pathophysiology (e.g., nociceptive versus neuropathic), its location (e.g., head and neck pain), or its putative mechanisms (e.g., tumor-related, treatment-related, pain unrelated to tumor or treatment).[126] Although these general categories are useful, more specific diagnostic criteria would allow more precise diagnosis with therapeutic implications and would enhance research efforts.

This lack of a unified taxonomy is not specific to cancer pain. Currently, there is an absence of evidence-based classification systems for most chronic pain conditions. [65] To meet this need, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION), a public-private partnership with the U.S. Food and Drug Administration and the American Pain Society (APS) collaborated to

develop the ACTTION-APS Pain Taxonomy (AAPT). The initiative worked to develop the characteristics of an ideal diagnostic system that would be biologically plausible, exhaustive, mutually exclusive, reliable, clinically useful, and simple through consensus conferences. The resulting diagnostic system includes 5 dimensions:

1. Core diagnostic criteria
2. Common features
3. Common medical comorbidities
4. Neurobiological, psychological, and functional consequences
5. Putative neurobiological and psychosocial mechanisms, risk factors, and protective factors. [65]

Following the establishment of these 5 dimensions, a working sub-group of clinical and basic scientists and clinicians with expertise in cancer pain was convened by the AAPT organizers. The aim of their effort was to apply the ideal framework of 5 dimensions developed during the original AAPT conference to cancer pain. The objectives included: (1) to identify chronic pain syndromes seen in oncology with high prevalence and significant impact and (2) to generate a classification system of diagnostic criteria for several of these syndromes based on these originally proposed 5 dimensions.

Methods

A working group of clinicians and clinical and basic scientists with expertise in cancer pain met during a consensus meeting held in July 2014. Group members from the United States and the United Kingdom were carefully selected based upon their contributions to the science and management of cancer pain, representing multiple disciplines (basic scientists, physicians, and nurses) with significant achievements in cancer-related epidemiology, research, and clinical care.

Prior to this meeting, a systematic review was conducted by two of the working group members (MM, MB) using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting system.[99] PRISMA is an evidence-based minimum set of items for reporting systematic reviews and meta-analyses. The databases searched included the following: the Cumulative Index to Nursing and Allied Health Literature (CINAHL) from 1981 to June 2014; the Cochrane Library of Systematic Reviews and the Cochrane Library of Controlled Trials from inception to June 2014; Database of Abstracts of Reviews of Effect from inception to April 2014; Embase Classic and Embase from 1947 to June 2014; Ovid MEDLINE® 1946 to June 2014; and OVID MEDLINE® In-Process and Other Non-Indexed Citations on June 11, 2014. These databases were searched for review articles (including summary reports, systematic reviews, and meta-analyses), as well as observational and experimental studies published in English. Articles were excluded if they did not describe the clinical characteristics of chronic cancer pain, including those that described animal studies, or were studies of acute or breakthrough cancer pain. Data were extracted and summarised descriptively with respect to the 5 AAPT diagnostic dimensions: (1) core diagnostic criteria, (2) common features, (3) common medical co-morbidities, (4) neurobiological, psychosocial and functional consequences, (5) putative neurobiological and psychosocial mechanisms, risk factors, and protective factors. Figure 1 illustrates the process employed in this systematic review. Key words included cancer pain, malignancy, chemotherapy, surgery, radiotherapy and neuropathy.

Bone pain, post-mastectomy pain, head and neck pain, neuropathic pain (disease related), and chemotherapy-induced peripheral neuropathy were most frequently referenced. These results were correlated with prevalence data of pain reported by tumor site, that generally demonstrate higher rates of pain reports in people with pancreatic, lung,

genitourinary, breast and prostate cancers.[20] The expert panel considered these and other pain syndromes aiming to initiate the process of taxonomy development with 3 syndromes before extending to the full range of cancer-related pain syndromes at a later time. The challenge in narrowing the selection to 3 syndromes was to achieve a balance between the most prevalent cancer pain syndromes versus areas that have received the most study and thus have the largest body of evidence. Ultimately guiding the selection was the aim to identify those syndromes with clinical or research utility (i.e., the painful conditions that are most homogeneous in terms of mechanism or presentation and offer the most relevant targets for further research).

Through working group discussion, debate and verbal consensus, 3 chronic pain syndromes seen as a result of cancer (i.e., bone pain and pancreatic cancer pain as a model of pain related to the tumor) or its treatment (chemotherapy-induced peripheral neuropathy) were unanimously selected. Head and neck pain was omitted because the source of this pain may be multifactorial (e.g., tumor, treatment related, or both) and diverse in relationship to specific anatomic location. Similarly, the working group agreed that disease-related neuropathic pain was too broad. While post-surgical pain syndromes, including post-mastectomy pain, were initially included, this group of pain conditions was omitted from the cancer-related pain taxonomy to avoid overlap with a broader discussion of post-surgical pain syndromes being conducted concurrently by a separate working group classifying neuropathic pain.

Then the cancer pain working group generated a classification for these syndromes based upon the AAPT multidimensional framework. This work was conducted during the consensus meeting and later refined through on-line discussion. To ensure that the references were timely, the entire literature review was updated as of January 2015. The

manuscript reporting these findings was written by several members (JAP, MM, MB) and reviewed, edited and approved by all members of the working group.

Results

Based on this qualitative review and after extensive discussion, the diagnostic criteria for 3 representative chronic cancer-related pain syndromes were developed collectively by the working group, including cancer-induced bone pain (CIBP), chemotherapy induced peripheral neuropathy (CIPN), and pancreatic cancer pain (PCP).

Cancer-Induced Bone Pain

It is estimated that 50-95% of all patients who die from cancer have bone involvement.[48, 132] The most common cancers to originate in the bone are osteosarcomas.[84] Cancers that frequently metastasize to bone include prostate, breast, lung, and myeloma.[6, 7, 14, 29, 38, 42, 47, 50, 52, 75, 87, 94, 106, 136] Of those with bone metastases, approximately 85% experience pain, with resultant immobility and reduced quality of life.[54] CIBP is a specific pain state with overlapping but distinct features of both acute nociceptive, inflammatory, and neuropathic pain processes.[61]

Dimension 1. Core diagnostic criteria of CIBP

The AAPT core diagnostic criteria for CIBP are summarized in Table 1. The history must include a cancer diagnosis and imaging evidence of bone disease consistent with primary or metastatic cancer.

Dimension 2. Common features of CIBP

The cardinal feature of CIBP is a mixture of continuous background pain (usually described as annoying, dull, gnawing, aching, and/or nagging) punctuated by evoked or spontaneous pain (often described as electric or shock-like) in one or more locations generally consistent with the given known distribution of bone lesions, associated with

weight bearing or movement or can occur spontaneously.[14, 22, 40, 43, 49, 61, 63, 72, 73, 85, 88, 92, 95, 113, 123, 125, 130, 132, 133, 140] Generalised bone pain can occur due to the presence of multiple bone lesions or resultant expansion of bone marrow from bone metastases.[27, 61] The distribution of the pain can be localised, radicular, or both.[73]

Typical sites of CIBP include the vertebrae (lower thoracic spine and lumbar regions are most prevalent), pelvis, long bones, and ribs.[27, 49] Bone lesions on the skull can result in headache pain due to calvarial, maxillary, or medullary lesions, as well as cranial nerve palsies such as mental nerve numbness or visual difficulties.[25, 27] Chest wall pain can occur as a result of bone lesions in the ribs.[27]

As the disease and tumor mass progress, the background pain increases in intensity and interference [61] and is generally responsive to opioid analgesics, alone or in conjunction with nonsteroidal anti-inflammatory drugs.[10, 22, 63, 71, 79, 112] Conversely, spontaneous pain (without specific eliciting stimuli) and evoked pain (i.e., in response to standing, weight bearing, movement, touch or other stimuli) associated with CIBP are difficult to treat from the onset due to their intermittent nature, which tends to be very rapid in onset, intense, and of short duration.[10, 22, 63, 71, 79, 112] Terminology commonly used in the clinical setting to describe evoked or spontaneous pain include breakthrough pain, incident pain or a pain flare; however, definitions for these terms often lack precision and may overlap. For example, breakthrough pain is defined as a transitory flare of pain in the setting of chronic pain managed with opioid drugs,[127] yet the evoked pain seen in CIBP can occur during weight bearing without current opioid use. The International Association for the Study of Pain (IASP) Taxonomy, the principal resource for definitions related to chronic pain, does not currently address evoked, breakthrough, incident, flare or spontaneous pain.

Dimension 3. Common medical comorbidities for CIBP

The primary comorbidity for CIBP is the presence of skeletal related events. These skeletal complications include pathological fractures of long bones, vertebrae, pelvis, rib, and other sites [11, 24, 25, 27, 28, 48, 51, 154] and in some cases spinal cord compression.[63, 73, 132], [56]

Dimension 4. Neurobiological, psychosocial, and functional consequences of CIBP

The consequences of CIBP can be serious because they affect biological, psychological, and functional aspects of the patient's life. [38, 73, 137] Although some pathologic fractures produce limited pain, primary or metastatic bone lesions affecting the femur, pelvis, or spine are likely to cause significant pain during standing or ambulation, resulting in reduced mobility.[63] Reduced quality of life and diminished activities of daily living are associated with CIBP.[41, 44, 48, 49, 91, 118, 132, 134, 160] Functional impairment is strongly associated with evoked or breakthrough pain.[92, 113] Fatigue is frequently reported in patients with metastatic bone disease and resultant pain.[133]

Depression is common in people with painful bone metastases and has been found to be significantly associated with impaired quality of life.[134] Additionally, the meaning of pain as a sign of advancing disease in those individuals with CIBP has been demonstrated to be correlated with increased pain intensity.[134] Anxiety in men with advanced prostate cancer is associated with increase pain intensity and number of metastatic bone lesions.[86] These studies reveal that the consequences of CIBP are not unlike those seen in chronic non-cancer pain syndromes, including impaired function, mood, and quality of life.[60, 155]

Dimension 5. Putative neurobiological and psychosocial mechanisms, risk factors, and protective factors for CIBP

CIBP is a mixed mechanism condition that includes elements of acute nociceptive pain, inflammatory pain, and neuropathic pain.[58, 61, 70, 103, 125, 132] Distinctive peripheral

modifications to bone and nervous tissues occur as well as neurobiological changes at the level of the spinal cord.[61, 70]

Acute nociceptive pain occurs due to localised bone destruction, which leads to loss of structural integrity and a decrease in pH. Cancer cells do not destroy bone directly, but rather they express the receptor activator of nuclear factor k-B ligand (RANKL), which binds to its receptor, RANK. Activation of the RANKL/RANK pathway stimulates the production of bone destroying osteoclasts.[103] Osteoclasts resorb bone by forming a highly acidic environment between the osteoclast and the bone. This stimulates the TRPV1 or ASIC3 channels expressed by a significant population of nociceptors that ultimately leads to the perception of incident pain with movement and weight bearing activities.[61]

Inflammatory pain develops when peripheral nerve endings in bone marrow and bone matrix are sensitized by localised inflammatory mediators stimulated by the cancer cells or their associated stromal cells. Locally released factors include bradykinin, endothelins, interleukin (IL)-6, granulocyte–macrophage colony-stimulating factor, nerve growth factor (NGF), proteases, and tumor necrosis factor (TNF)-a.[103] This change is generally associated with steady background pain.[61]

Neuropathic pain results from compression, distension, increase in sprouting, or denervation of nerve endings and/or axonal structures caused by expansion of the tumor. These changes lead to spontaneous pain and associated altered sensations.[61]

Nociceptive and neuropathic mechanisms work in concert to produce a complex mixture of ongoing acute, inflammatory and neuropathic processes. These processes lead to a hyper-excitable state within the spinal cord, which itself is associated with amplification and modification of noxious and non-noxious peripheral stimuli.[61, 70, 156]

Interventions to protect against CIBP have been developed based upon current understanding of the underlying neurobiology. Bisphosphonates bind to bone, interfering with osteoclast function, later resulting in osteoclast apoptosis.[103] Osteoprotegerin or denosumab, therapies that interfere with RANKL binding to RANK deplete activated osteoclasts, reduce signs of bone resorption, and diminish bone cancer pain.[146] This is a rapidly evolving area of research and numerous studies are underway to examine compounds that might block CIBP.[146] Regarding putative psychosocial mechanisms associated with CIBP or other risk factors, little is currently understood and additional research is warranted.

Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy induced peripheral neuropathy (CIPN) is a serious treatment induced toxicity that can limit function, impair quality of life, and in some cases, diminish the potential for cure when chemotherapy doses need to be reduced. [9] This condition is increasing in prevalence as greater numbers of neurotoxic agents are introduced and as patients live longer with the consequences of neuropathy. In a recent systematic review of 31 studies with data from 4179 patients, CIPN prevalence was 68.1% (57.7–78.4) in the first month after chemotherapy, 60.0% (36.4–81.6) at 3 months and 30.0% (6.4–53.5) at 6 months or later.[141]

Dimension 1. Core diagnostic criteria of CIPN

CIPN occurs in oncology patients when treatment involves a neurotoxic agent. A temporal relationship exists between the onset of symptoms and the starting, stopping, and duration of therapy.[34, 37, 46, 62, 78, 148] Peripheral sensory and motor nerve damage or dysfunction are the putative mechanisms for CIPN.[36, 37, 62, 101, 121, 148, 151, 162]

CIPN poses a significant challenge for the patient and clinician in terms of diagnosis, management and associated reductions in function and quality of life, particularly in patients with coexisting conditions or disorders that involve the peripheral nervous system (e.g., diabetes, HIV).[2, 33, 68, 78, 80, 81, 104, 120, 121, 148, 151] Table 2 lists the core diagnostic criteria for CIPN.

Dimension 2. Common features of CIPN

The cardinal feature of dose-limiting CIPN is a gradually-progressive distal symmetrical sensory neuropathy (stocking/glove distribution), which may be associated with diminished motor function. However, more often than not motor symptoms are absent until later stages of CIPN.[3, 13, 36, 37, 62, 78, 80, 101, 121, 148, 151, 162] Neuropathy in the feet without involvement in the hands is common. In addition to descriptors such as "tingling" or "burning", patients often describe these sensory abnormalities with terms such as "discomfort" or "unpleasant". Cramping, more common in the lower limbs, may be reported.[151]

Clinical examination reveals sensory loss to one or more sensory modalities and/or evoked pain in a stocking and glove distribution. These findings include hypoesthesia (a bilateral increase in detection thresholds to tactile, vibration, or non-noxious warm or cool stimuli)[53, 57, 78], or hypoalgesia (a bilateral increase in pain detection thresholds to blunt pressure or pinprick stimuli)[53, 57, 78], or hyperalgesia (a bilateral decrease in pain detection threshold to noxious heat or cold stimuli.)[18, 53] The anatomic distribution of these physical examination findings may not correspond exactly to the sensory symptoms.[2, 30, 46, 53, 78, 80, 109, 115, 120, 148, 152, 158, 162]

Signs and symptoms of CIPN, including pain, commonly begin in the lower extremities followed by the upper extremities and progress proximally.[78] However, not all

go on to experience neuropathy in the upper extremities. The temporal features of CIPN are rapid onset (hours or days) of sensory abnormalities following initiation of neurotoxic chemotherapy.[78, 101] In the majority of cases, the onset of CIPN symptoms and signs is progressive; beginning with mild paraesthesias in the lower extremities, becoming progressively more intense, and advancing proximally with cumulative dose exposure.[78, 101]

Some patients may experience a reduction in the intensity of symptoms between treatment cycles – sometimes referred to as a waxing and waning effect.[122] In some cases, symptoms and signs of CIPN may continue or worsen after treatment has ended, a phenomenon known as 'coasting'.[37, 78, 101] Increasing evidence suggests that pre-existing sensory deficits (clinical or sub-clinical neuropathy) are associated with the onset of more extensive and severe CIPN symptoms and signs.[18, 53] The prevalence of autonomic changes associated with CIPN is poorly understood, but can include serious complications such as falls related to orthostatic hypotension.[1]

Agents most likely to result in CIPN include platinum based drugs (e.g., cisplatin, carboplatin, and oxaliplatin), vinca alkaloids (e.g., vincristine, vinblastine), taxanes (e.g., paclitaxel, docetaxel), bortezomib, thalidomide, lenalidomide, eribulin, and ixabepilone. The frequency and severity of CIPN is generally related to the specific drug, dose, schedule (e.g., more prevalent with weekly versus every 3 week dosing of paclitaxel), speed of administration, and duration of therapy.[111] In the case of bortezomib, route of delivery affected the prevalence of CIPN. Peripheral neuropathy of any grade was significantly less common with subcutaneous bortezomib administration compared to intravenous delivery.[114]

Sensations described by patients vary with the administered chemotherapeutic agent. In a recent prospective study that compared the experience of patients receiving

docetaxel versus oxaliplatin, tingling was the most common symptom experienced by both groups, yet pain and discomfort associated with cold was uniquely reported by those who received oxaliplatin.[157]

Motor weakness, with a similar peripheral distribution to sensory alterations, can occur in CIPN, but overall is observed less frequently than sensory abnormalities.[62, 101, 141] However, patients frequently demonstrate a decrease in mechano-sensory function, as measured by a timed pegboard test or the time taken to button a shirt.[16, 17, 128] Importantly, impaired proprioception is reported by many patients with CIPN, described as feeling unbalanced, particularly in the absence of visual cues when walking or standing (e.g., in dark settings, when closing one's eyes in the shower).[78, 116] Clinical examination may reveal a positive Romberg sign and generalised ataxia in more severe cases.[124] Symmetrical loss of deep tendon reflexes (Achilles or brachioradialis) is a sign of more advanced CIPN.[78]

Dimension 3. Common medical comorbidities of CIPN

People at greatest risk for CIPN are believed to include those with comorbid conditions known to contribute to neuropathy, including diabetes, obesity, and HIV, .[81, 128, 141] Pharmacogenetic profiling of genetic polymorphisms has been conducted to identify susceptibility to CIPN based on genetic polymorphisms. For example, polymorphisms in the *CYP2C8* and *CYP3A5* genes that encode for paclitaxel metabolizing enzymes were found to be associated with CIPN.[31, 82] Even though pharmacogenetic profiling may one day identify patients at greater risk for severe CIPN, the data so far are insufficient to draw any definitive conclusions.

Dimension 4. Neurobiological, psychosocial, and functional consequences of CIPN

Terminal axonal degeneration and axonal microtubule disruption are the most common pathophysiologic consequences observed in CIPN.[78] Psychosocial consequences of

CIPN include depression, anxiety, impaired sleep and other mood changes.[69, 83, 151, 157] The functional outcomes of CIPN range from mild symptoms which do not interfere with activities of daily living (ADL) to moderate and severe dose-limiting sensory and motor alterations that interfere with ADLs .[32, 34-37, 131] The need to limit doses of chemotherapy due to CIPN can lead to shortened survival. In the most severe cases sensory and motor alterations are disabling, resulting in paralysis, complete loss of function, or both.[101, 104, 147]

Dimension 5. Putative neurobiological and psychosocial mechanisms, risk factors, and protective factors for CIPN

The underlying pathophysiologic mechanism(s) that lead to the development of CIPN are not completely understood. Nevertheless, the similarity in the pattern and spectrum of clinical symptoms and signs of CIPN caused by different chemotherapeutic agents is apparent. Common underlying mechanisms purported to be involved in the development of CIPN are: [5, 12, 23, 62, 77, 119, 122, 152, 161, 162]

- Disruption of axoplasmic microtubule-mediated transport causing distal axonopathy, a known cellular effect of many chemotherapy agents
- Distal axonal degeneration
- Direct damage to sensory nerve cell bodies of the dorsal root ganglia
- Mitochondrial dysfunction
- Activation of protein kinases and extracellular kinases (associated with cisplatin-induced CIPN)
- Oxaliplatin is associated with actual nerve cell death and decreased epidermal nerve fiber density with each cycle, as well as decreased conduction velocity and amplitude
- Alteration of gene expression thought to be involved in pain mediation in spinal cord dorsal horn (associated with vincristine exposure)

- Decrease in the density of grey matter after one month in women with breast cancer experiencing CIPN
- Central sensitization as a consequence of long-term peripheral nerve injury

A recent systematic review explored risk factors for CIPN and found the following elements: baseline neuropathy, smoking, abnormal creatinine clearance and distinct sensory changes during chemotherapy treatment, including cold allodynia and cold hyperalgesia.[141] Sensory changes during chemotherapy treatment, including increased pain and neuronal hyperexcitability, are also predictors of CIPN.[141] A prospective study of patients receiving oxaliplatin and followed for 1 year found that those patients with elevated heat detection thresholds (higher temperature levels were needed to perceive heat) before receiving chemotherapy were more likely to experience intense CIPN.[128]

Few protective factors for CIPN have been identified. A recent investigation employed large Medicare claims data and found that a history of autoimmune disease was associated with reduced risk of CIPN.[81] Regarding prevention of CIPN, a recent clinical practice guideline from the American Society of Clinical Oncology reviewed existing evidence. After extensive analysis, the authors were unable to recommend any agents to prevent this syndrome due to the lack of high quality evidence.[80]

Pancreatic cancer pain

The estimated incidence of pancreatic cancer for 2016 is more than 53,000 in the U.S., with approximately 42,000 dying from this disease.[144] Risk factors for pancreatic cancer include family history, obesity, smoking, and chronic pancreatitis.[89, 145, 149] Upper abdominal pain is a common presenting symptom of pancreatic cancer. The prevalence of pain associated with pancreatic cancer ranges from 72-100%.[15]

Dimension 1. Core diagnostic criteria of PCP

Pancreatic cancer pain occurs in the presence of a diagnosis of pancreatic cancer confirmed by imaging evidence of an epigastric mass and/or biopsy that establishes the diagnosis. Table 3 presents the core diagnostic criteria.

Dimension 2. Common features of PCP

The cardinal features of pancreatic cancer pain are upper abdominal pain with frequent extension to the back, either to the low back or the region between the scapulae spreading laterally, and unexplained weight loss.[143] Less frequently PCP is diffuse within the abdomen or referred to the lower abdominal quadrants.[26, 90] The pain is often described as dull, aching, gnawing or spasmodic [26, 143] and the intensity can fluctuate throughout the day with position (e.g., exacerbated by supine positioning) and food ingestion.[143] Pain intensity usually increases with disease severity. However, because this cancer is often diagnosed late, 20-30% of patients report moderate to severe pain at diagnosis.[26] The back pain associated with PCP may be worse when the patient is supine and eased by sitting forward.[26, 90, 143]

Dimension 3. Common medical comorbidities of PCP

Jaundice and dark urine can be a presenting symptom in cancers of the pancreatic head.[143] Unexplained weight loss, anorexia, diabetes, and other sequelae of pancreatic cancer or its treatment are common.[15, 90, 143] To date, few medical comorbidities of pancreatic cancer pain have been identified.

Dimension 4. Neurobiological, psychosocial, and functional consequences of PCP

Because pancreatic cancer is highly associated with pain, it is difficult to discern whether other symptoms are related to the cancer or pain. Several studies have documented a very high prevalence of depressed mood in those patients with pancreatic

cancer, higher than other cancers with similar prognoses.[8, 26, 45] Symptom burden in general is high in this population, notably including disturbed sleep and fatigue[90] as well as nausea and vomiting associated with obstruction or delayed gastric emptying.[15]

Dimension 5. Putative neurobiological and psychosocial mechanisms, risk factors, and protective factors for PCP

Pain occurs in 90% of patients with cancer of the head of the pancreas and is much less common in cancer of pancreatic body or tail.[26, 64, 143] Back pain often indicates that retroperitoneal or celiac plexus infiltration has occurred.[143] Putative mechanisms include compression or infiltration (perineural invasion) of splanchnic nerves in the celiac plexus by direct local tumour expansion,[8, 19, 117, 143] as well as compression of surrounding tissues and organs. Celiac plexus block has been found to be effective in relieving PCP.[4, 107, 135] It is unclear if relief signifies extension of tumor into the plexus, or interruption of visceral afferent neurons that are also found in the plexus. No other risk factors or protective factors for PCP could be identified.

Discussion

Cancer-related pain remains a complex, multidimensional phenomenon. The exercise of developing a standardized, rigorous, valid taxonomy for just 3 common cancer pain syndromes revealed the limitations in our existing nomenclature. Current studies attempting to characterize and establish prevalence rates for specific cancer pain syndromes are hampered by the absence of explicit definitions. A clear example is the large, prospective study by Ventzel and colleagues comparing neuropathy characteristics in patients receiving oxaliplatin versus docetaxel.[157] Although the prevalence of pain in the hands and feet was approximately equal between the 2 groups, on further analysis, a significant percentage of those treated with docetaxel reported less burning and numbness,

suggesting the pain was not consistent with CIPN. The investigators postulated this difference may be related to the use of adjuvant endocrine therapies, such as the aromatase inhibitors, often prescribed for those who have received docetaxel. These endocrine therapies are known to cause arthralgias, myalgias and carpal tunnel syndrome.[110, 142] The investigators used a variety of questionnaires to determine these differences, yet not all clinicians or researchers will be able to employ such an extensive battery of measures. It is our hope that the core diagnostic criteria will help future investigators to not only better characterize cancer pain syndromes, as was done in this study, but to differentiate them from related phenomenon to avoid inaccurate interpretations.[100]

The consequences of cancer pain can be significant, including deleterious effects on function, mood, sleep, fatigue, and ultimately, quality of life. [60, 155] Additionally, increased intensity of cancer pain is associated with heightened suffering in those at end of life.[159] Finally, studies support the association between pain and reduced survival, demanding more urgent attention to this symptom. [76, 129] More research is warranted to discern the neurobiological, psychological, and functional consequences of each of these and other cancer pain syndromes.

Another area that demands additional study is the determination of the mechanisms of cancer pain. While important work has begun in the area of CIBP, [39, 102, 103, 105] CIPN,[66, 74, 97, 98] and PCP, [55, 93] additional research is needed to elucidate the neurobiological factors responsible for cancer pain. An exciting line of investigation is the interactions among the cancer microenvironment, the primary afferent nociceptor, and the immune system.[138, 139]

An additional area of clarification relates to risk factors and protective determinants for cancer pain. Early research exploring cancer pain focused on clinical or biological factors, such cancer diagnosis, stage of disease, or treatment. In recent important work, Miaskowski and colleagues found that cancer patients with the highest symptom burden were significantly younger, more likely to be female and non-white, had lower levels of social support, lower socioeconomic status, poorer functional status, and a higher level of comorbidity.[108] In a large study of people with breast cancer, colorectal cancer or prostate cancer, Lewis et al. found that factors associated with more severe CIPN included colon versus other cancers, the duration and type of therapy, poor socioeconomic status and black race. [96] Factors influencing cancer pain must be expanded in future studies, including psychosocial factors[60] and overlapping chronic pain conditions and comorbidities.[100] Additionally, identification of genetic polymorphisms might allow for the identification of those at risk for these painful syndromes, as well as direct prevention and treatment innovations.

Finally, an emerging area of research that requires further investigation is the development of phenotypic profiles of cancer pain syndromes based on symptoms and clinical signs. Recent studies in non-cancer chronic pain syndromes (such as diabetic peripheral neuropathy) suggest that stratification of patients into homogeneous groups based on symptom profiles may be advantageous for analgesic drug trials and ultimately lead to a more targeted approach to cancer pain management.[67, 150]

This proposed taxonomy presents early work in developing a classification system for cancer related pain conditions. Current classification systems focusing on duration (acute versus chronic) or presumed etiology (related to the cancer, related to treatment, or

unrelated) do not provide the specificity needed to clearly define distinct cancer pain syndromes. There were numerous challenges in the development process, notably limitations in existing research related to cancer pain. Studies are often hampered by a wide array of weaknesses, including heterogeneous populations, small sample sizes, dissimilar assessment tools and techniques, and inadequate duration of investigations. Although the working group strove to identify diagnostic criteria that were absolutely necessary to describe each painful syndrome, once these criteria are applied more broadly, controversy will arise and modification will likely be indicated. Future work will now be required to validate this proposed taxonomy in populations of people with cancer and determine the feasibility of its use in both clinical and research settings. Investigators studying these 3 syndromes should incorporate the core diagnostic criteria when employing research methods. Clinicians may find the use of the criteria of benefit when considering the differential diagnosis of complex cancer pain syndromes. This current undertaking classified just 3 syndromes; much additional work is needed to characterize the many other painful syndromes that occur in those individuals diagnosed with cancer.

Conclusions

Three cancer pain syndromes, 2 related to cancer, and one related to a common cancer treatment, were classified using the AAPT multidimensional chronic pain taxonomy. Future work will demonstrate the validity and reliability of these proposed diagnostic criteria. [21] As our understanding of these cancer pain conditions matures, it is expected that the taxonomy will expand and evolve. It is the hope of this working group that classification of these cancer pain syndromes will ultimately strengthen clinical, scientific and educational efforts around cancer pain. Transforming our understanding of cancer pain is urgently

needed to improve its management as well as improve patients' relief and survivors' quality of life.

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Legend

Figure 1. PRISMA diagram

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is an evidence-based minimum set of items for reporting systematic reviews

Table 1. Dimension 1: Core Diagnostic Criteria for CIBP

1. History of primary or metastatic bone cancer diagnosed by imaging and physical examination
2. Presence of continuous, background pain (usually described as annoying, dull, gnawing, aching, and/or nagging) in one or more locations generally consistent with known distribution of bone lesions[40, 41, 43, 49, 50, 61, 92, 133]
3. Presence of evoked or spontaneous pain (often described as electric or shock-like) in one or more locations generally consistent with known distribution of bone lesions, associated with weight bearing or movement or can occur spontaneously[40, 41, 43, 48-50, 61, 85, 92, 133]
4. Clinical examination over the site of pain reveals:
    - Hyperalgesia to blunt,non-noxious pressure or pin-prick stimuli or
    - Hypoesthesia to non-noxious thermal stimuli or
    - Hypoesthesia to light touch stimuli[140]

Table 2. Dimension 1: Core Diagnostic Criteria for CIPN

1. Onset of pain following exposure to a chemotherapeutic agent known to be neurotoxic
2. Presence of painful symptoms in a symmetrical stocking and glove distribution beginning in lower extremities which may progress to the upper extremities, although finding in the feet and not in the hands are common
3. Painful symptoms are accompanied by non-painful symptoms (e.g., "pins and needles" or numbness) in a similar distribution.
4. Clinical examination reveals sensory loss to one or more sensory modalities and/or evoked pain in a stocking and glove distribution, as reflected in at least one of the following:
   - Hypoesthesia – bilateral increase in detection thresholds to tactile, vibration, or non-noxious warm or cool stimuli or
   - Hypoalgesia – bilateral increase in pain detection thresholds to blunt pressure or pinprick stimuli, or
   - Hyperalgesia – bilateral decrease in pain detection threshold to noxious heat or cold stimuli
5. Magnitude of the sensory abnormalities is disproportionately greater than the magnitude of any motor abnormalities in the affected region (except in the case of neuropathy after vinca alkaloids)
6. No other condition (e.g., polyneuropathy of other origin) could plausibly account for painful symptoms

Table 3. Dimension 1: Core Diagnostic Criteria for PCP

1. History of pancreatic cancer diagnosed by imaging, physical examination, and in some cases biopsy and laboratory analysis of blood or tissues for tumor markers
2. Presence of pain in upper abdominal region (typically referred to the epigastric region or upper abdominal quadrants) spreading posteriorly and/or radiating to the back
3. On clinical examination, the patient displays tenderness on upper abdominal palpation
4. No other condition (e.g., constipation) could plausibly account for persisting pain in the upper abdomen

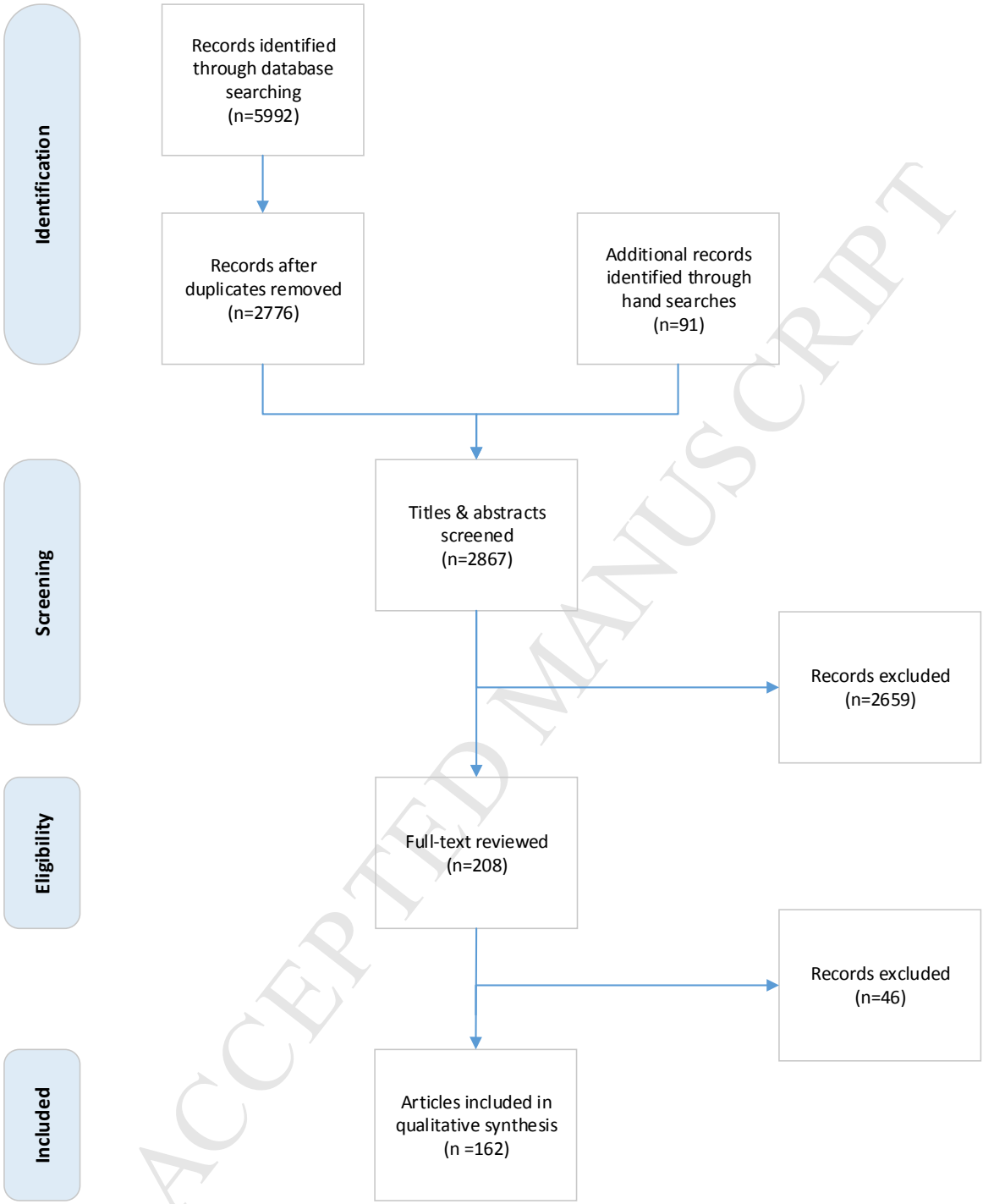

Figure 1. PRISMA diagram

AAPT Diagnostic Criteria for Chronic Cancer Pain Conditions

Highlights

- No comprehensive, universally accepted cancer pain classification system currently exists.
- An evidence-based taxonomy would enhance cancer pain research efforts by providing consistent diagnostic criteria, ensuring comparability across clinical trials.
- As part of a collaborative effort between the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) and the American Pain Society (APS), the ACTTION-APS Pain Taxonomy (AAPT) initiative worked to develop the characteristics of an optimal diagnostic system for cancer pain.
- Diagnostic criteria were developed for three chronic pain syndromes associated with cancer (i.e., bone pain and pancreatic cancer pain as models of pain related to a tumor) or its treatment (i.e., chemotherapy-induced peripheral neuropathy). Future efforts will subject these diagnostic categories and criteria to systematic empirical evaluation of their feasibility, reliability and validity and extension to other cancer-related pain syndromes.