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Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification

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Abstract: **There is increasing recognition that many if not most common chronic pain conditions are heterogeneous with a high degree of overlap or coprevalence of other common pain conditions along with influences from biopsychosocial factors. At present, very little attention is given to the high degree of overlap of many common pain conditions when recruiting for clinical trials. As such, many if not most patients enrolled into clinical studies are not representative of most chronic pain patients. The failure to account for the heterogeneous and overlapping nature of most common pain conditions may result in treatment responses of small effect size when these treatments are administered to patients with chronic overlapping pain conditions (COPCs) represented in the general population. In this brief review we describe the concept of COPCs and the putative mechanisms underlying COPCs. Finally, we present a series of recommendations that will advance our understanding of COPCs.**

Perspective: ***This brief review describes the concept of COPCs. A mechanism-based heuristic model is presented and current knowledge and evidence for COPCs are presented. Finally, a set of recommendations is provided to advance our understanding of COPCs.***

Key words: *Overlapping conditions, diagnosis, classification, pain sensitivity, psychological factors, genetic factors.*

The 2011 Institute of Medicine report on "Relieving Pain in America"[19] highlighted the magnitude and significance of chronic pain to the American public. The report noted the increasing recognition that some common or highly prevalent chronic pain conditions appear to coexist, and these coexisting conditions appear to be more prevalent in women compared with men. The concept of coexisting pain conditions has been recognized by the National Institutes of Health and the US Congress as a set of disorders that coaggregate and include, but should not be limited to, temporomandibular disorder (TMD), fibromyalgia (FM), irritable bowel syndrome (IBS), vulvodynia, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, chronic tension-type headache, migraine headache, and chronic lower back pain. Collectively, these conditions are increasingly referred to as chronic overlapping pain conditions (COPCs).[115]

Recently, Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) and the American Pain Society (APS) proposed a framework for classification of chronic pain conditions, known as the ACTTION-APS Pain Taxonomy (AAPT).[33] AAPT working groups are currently applying

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the taxonomy by developing diagnostic criteria for most common chronic pain conditions, including those listed previously that often coexist as COPCs. Although the AAPT criteria will be specific to individual pain conditions, clinicians and investigators will also need to consider COPCs in their application of AAPT for classification of patients. This brief overview will discuss epidemiological approaches and principles that help conceptualize and define COPCs, and we will describe putative etiological processes that underlie clinical manifestations of COPCs. Also, we will consider the implications of COPCs for the development and implementation of the AAPT taxonomy.

Epidemiology of COPCs

Epidemiology is concerned with the distribution and determinants of illness in human populations. All 4 key words in this definition merit critical appraisal in the context of COPCs.

The distribution of illness is measured most commonly as prevalence and incidence. Prevalence represents the proportion of people in a defined population who have the illness at a defined time. Conceptually simple, prevalence is typically measured using cross-sectional studies. Aggregated across such studies, the prevalence of individual COPCs ranges from 4 million (myalgic encephalomyelitis/chronic fatigue syndrome) to 44 million (IBS).[115] Incidence is the rate at which illness develops in a population, making it more challenging to measure than prevalence in part because of the requirement for a longitudinal design and needing to deal with illnesses that can remit, recur, or alter in severity—hallmarks of most COPCs. For example, the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) prospective cohort study investigated onset of painful TMD in US adults who had no previous experience of the condition when enrolled. Symptoms of the condition were evaluated prospectively, once every quarter. During a median 3-year follow-up period, one-third of study participants developed symptoms in at least one of the quarters, and approximately one-third of those individuals experienced recurrence.[98] Overall, 1 in 10 developed examiner-verified painful TMD.[95]

Determinants refer to the causes of illness in a population. Concepts of causation are inherently more complicated than descriptions of the distribution of illness. In principle, the best evidence of causation would come from an experimental study design in which people are assigned at random to be exposed or not exposed to a putative cause. Although such a design would be feasible for something that prevents disease, it would not be ethically acceptable to expose people to a putative risk of a disease. Instead, we must rely on rigorously designed observational studies.[49] In the case of COPCs, many are defined as being "idiopathic," as not being able to be explained by injury or pathology in the tissues from which the pain originates, or both.[23] For COPCs, aspects of the biopsychosocial model have been proposed to account for their occurrence.[17,123]

Another fundamental problem arises in defining the illness itself. The very starting point for any epidemiologic study is a "case definition" of the illness under study, so that those with the illness can be counted systematically when determining, say, prevalence in a population. For many individual COPCs, the task of case definition has been aided considerably in recent decades thanks to consensus-derived, evidence-based case classifications (Table 1). However, there are no such case classifications for COPCs as a whole nor is there unanimity regarding the causes of overlap. This problem is not unique to pain research. For example, one systematic review of evidence for overlap of unexplained clinical conditions reported that many instances of overlap were simply due to applying the same criteria (eg, "fatigue") to 2 or more clinically distinct syndromes.[1] These authors concluded "The diagnosis assigned to patients with … these [unexplained] illnesses depends more on the chief symptom and clinician specialty than the actual illness." In principle, the problem can be circumvented in epidemiologic studies when all selected COPCs are evaluated independently, on the basis of accepted criteria for each condition. The latter, however, begs the question as to which COPCs should be evaluated. If the goal is to determine comorbidity, defined as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study,"[31] then the list could extend well beyond conditions that are primarily painful to include physical diagnoses such as hypertension, mental health conditions such as depression, or aspects of social health. For

Table 1. Current Approaches to Classifying/Diagnosing Each COPC

Condition	Approach
Fibromyalgia	ACR 1990[129]
	ACR 2010[128]
	Survey Criteria[127]
Irritable bowel syndrome	ROME III[26]
TMD	TMD Screener[38]
	DC/TMD 2014[92]
ME/CFS	CDC 1994 (CFS)[35]
	Revised Canadian 2010 (ME/CFS)[53]
	IOM 2015 (SEID)[18]
Tension headache	ICHD III[47]
Migraine headache	ICHD III[47]
Chronic low back pain	NIH Task Force[20]
Endometriosis	Epidemiology case definition[52]
IC/PBS	NIDDK[54]
Vulvodynia	Screening[46,86]
	Consensus statement due out 2015

Abbreviations: COPC, chronic overlapping pain condition; ACR, American College of Rheumatology; ROME III, ROME III irritable bowel syndrome diagnostic guidelines; TMD, temporomandibular disorders; DC, diagnostic criteria for temporomandibular disorders; ME, myalgic encephalomyelitis; CFS, chronic fatigue syndrome; CDC, Centers for Disease Control and Prevention; IOM, Institute of Medicine; SEID, systemic exertion intolerance disease; ICHD, International Classification of Headache Disorders; NIH, National Institutes of Health; IC/PBS, interstitial cystitis/painful bladder syndrome; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases.