

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.

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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.

simplicity, we start with the 10 diagnostic entities listed earlier but empirical investigation may expand this list over time.

The population under study is a critical component of any epidemiologic study, but the apparent simplicity of the concept can be misleading. A 1946 study¹⁰ of overlapping health conditions provided a classic illustration of bias that can be created when making inferences about etiology in the population at large using data from a study of a different population. In the study, Berkson used basic principles of probability to investigate an apparent relationship between cholecystic disease and risk of diabetes mellitus that had been documented in studies of hospital patients. At the time, gall bladders were being removed because cholecystic disease was a suspected cause of diabetes in the population at large because it was seen frequently in patients with diabetes. Berkson showed that the statistical association observed in hospital patients was spurious because of selection bias in which multiple diagnoses are more common in the hospital than in the general population.¹⁰ The lesson is relevant 7 decades later; if we want to learn about etiologic contributions underlying COPCs in the population, it is critical to conduct epidemiologic studies in samples selected at random from the population, not from hospital patients.

The remaining parts of this section report findings from our analysis of publicly available data from the National Health Interview Survey (NHIS). The survey, conducted annually by the National Center for Health Statistics, selects a nationally representative sample of the civilian, noninstitutionalized population of the United States. The survey uses a multistage, stratified, clustered sampling design that covers the 50 states

and the District of Columbia, selecting approximately 40,000 households. Interviews are conducted with approximately 100,000 people, with oversampling of African American, Hispanic, Asian, and elderly minorities. The face-to-face, computer-assisted personal interviews take approximately 1 hour and are conducted by trained interviewers from the US Census Bureau. The survey participation rate has exceeded 85% in recent decades.

For the current report, we analyzed the NHIS data set from the 2009 survey, restricting the analysis to people aged 18 years or older. Case definitions were therefore on the basis of a positive response to each of the self-reported questions about pain in the back, head, neck, or jaw/face (Fig 1). Case classification of joint pain was on the basis of self-reported pain at 2 or more nonaxial joints. Jaw or face pain was selected as the “index” pain condition, and the goal was to analyze its extent of overlap with the other pain symptoms. This is consistent with the concept of comorbidity which, by necessity, begins with selection of an index condition.³¹ Although this is a useful way to illustrate features of overlapping pain in the US population in this article, it should be noted that the choice of an index condition varies according to the research question and the health care setting, and hence is not self-evident.¹¹³ Five percent of US adults reported jaw or face pain in the preceding 3 months, representing 11.5 million adults (Table 2). Neck pain and severe headache or migraine each had prevalence of approximately 15%, whereas back pain was the most common of the pain conditions, with prevalence of 28.5%.

Jaw/face pain overlapped considerably with headache and neck pain (Fig 2). People with 1 of those conditions

The following questions are about pain you may have experienced in the PAST THREE MONTHS. Please refer to pain that LASTED A WHOLE DAY OR MORE. Do not report aches and pains that are fleeting or minor. During the PAST THREE MONTHS, did you have:

- Facial ache or pain in the jaw muscles or the joint in front of the ear?
- Severe headache or migraine?
- Neck pain?
- Back pain? If yes: did this pain spread down either leg to areas below the knees?

Response categories: Yes; No; Refused; Don't know

The next questions refer to your joints. Please do NOT include the back or neck. DURING THE PAST 30 DAYS, have you had any symptoms of pain, aching, or stiffness in or around a joint?
Response categories: Yes; No; Refused; Don't know

If yes, which joints were affected?

<input type="checkbox"/> Shoulder-right	<input type="checkbox"/> Shoulder-left	<input type="checkbox"/> Elbow-right	<input type="checkbox"/> Elbow-left
<input type="checkbox"/> Hip-right	<input type="checkbox"/> Hip-left	<input type="checkbox"/> Wrist-right	<input type="checkbox"/> Wrist-left
<input type="checkbox"/> Knee-right	<input type="checkbox"/> Knee-left	<input type="checkbox"/> Ankle-right	<input type="checkbox"/> Ankle-left
<input type="checkbox"/> Toes-right	<input type="checkbox"/> Toes-left	<input type="checkbox"/> Fingers/thumb-right	
<input type="checkbox"/> Fingers/thumb-left	<input type="checkbox"/> Other joint not listed		

Figure 1. Questions about pain asked in the 2009 National Health Interview Survey.

Table 2. Prevalence of 5 Self-Reported Pain Symptoms, US Adults, 2009

SYMPTOM	PEOPLE, %	PEOPLE (MILLIONS), N
During past 3 mo		
Back pain	28.5	64.8
Severe headache/migraine	15.8	36.0
Neck pain	15.4	35.0
Jaw/face pain	5.1	11.5
During past 30 d		
≥2 Nonaxial joints aching/painful	23.4	53.2

had approximately twice the expected prevalence of jaw/face pain, whereas people with both of them had 5.6 times the expected prevalence of jaw/face pain. There was weaker overlap between jaw/face pain and each of back pain and nonaxial joint pain, although co-occurrence of the 2 types of body pain was associated with threefold greater prevalence of TMD than expected.

There was also considerable similarity in the sociodemographic distribution of jaw/face pain, headache, and neck pain (Fig 3). Each peaked in prevalence at approximately the fifth decade of life, and was more frequent in women compared with men. The prevalence of each was greatest in Native American and least in Asian individuals, although differences between Hispanic and non-Hispanic individuals were small. Each exhibited large, inverse associations between income and prevalence. In contrast, back pain prevalence increased with age, was only marginally greater in women compared with men, and there was a less pronounced income gradient in its prevalence.

Another way to quantify the overlap is to count the number of pain conditions reported by each person (Table 3). Of the estimated 21.9 million US adults who reported 3 or more of headache, neck pain, back pain, or nonaxial joint pain, 23.4% also reported jaw/face pain. That represents 26.5 times the odds of jaw pain relative to people who reported none of the other pain conditions. Although less pronounced, there was also overlap

of jaw pain and medical conditions that are not primarily painful (Table 4). Adults who reported 3 or more of 12 health conditions had 4.9 times the odds of jaw/face pain relative to adults who reported none of those health conditions.

When interpreting these findings, it is important to note limitations that are inherent in self-reported symptoms collected in population-based surveys. Conversely, the population-based sampling rigor of the NHIS precludes the possibility of selection biases, such as Berksonian bias, as an explanation for the overlap observed in our analysis. And although this analysis arbitrarily focused on jaw and face pain as the “index” condition, the degree of overlap is consistent with findings from a systematic review of overlap in unexplained clinical conditions.¹

There are 3 main implications from this brief investigation of pain symptoms in the US population. First, using jaw pain as the “index” pain symptom, there was considerable overlap with 4 selected sets of pain symptoms. Although the overlap was most pronounced for other pain experienced above the shoulders (headache, neck pain), there was significant overlap with symptoms in the back and in nonaxial joints. As discussed in the Etiology and Mechanisms section, this degree of anatomical dispersion of symptoms is consistent with predominant models that explain overlap as a consequence of disruption of central pain regulatory systems. Second, sociodemographic patterns of variation in pain symptom prevalence were strikingly similar for jaw pain, headache, and neck pain, although not for back pain. Conventionally, those sociodemographic characteristics are not regarded as etiologic mechanisms responsible for overlap, which raises the intriguing question as to whether searches for such mechanisms should statistically adjust for background sociodemographic characteristics (eg, through age standardization). Third, there was some degree of overlap between jaw pain symptoms and self-reported medical conditions that are not primarily painful. This is consistent with the intriguing concept that overlapping pain conditions and underlying disruption of central pain regulatory systems are responses that are harnessed to combat pathology.⁴²

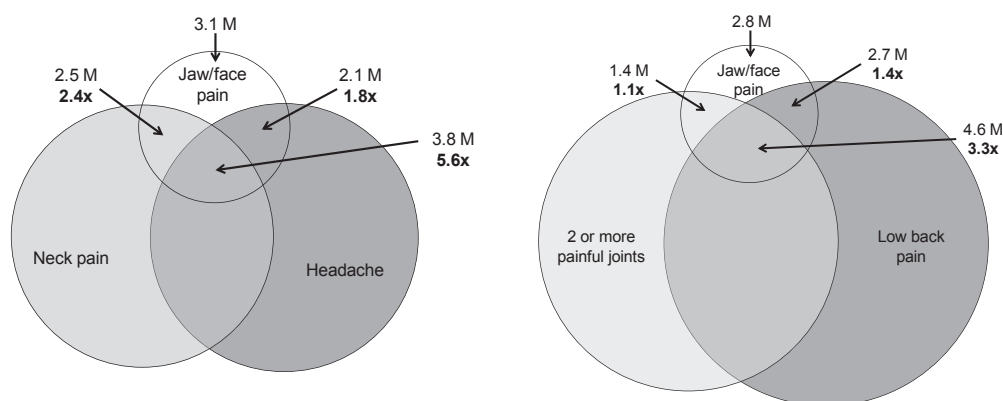


Figure 2. Venn diagram depicting overlap of jaw/face pain and other painful conditions, US adults, 2009. Source: the authors' analysis of the 2009 National Health Interview Survey.

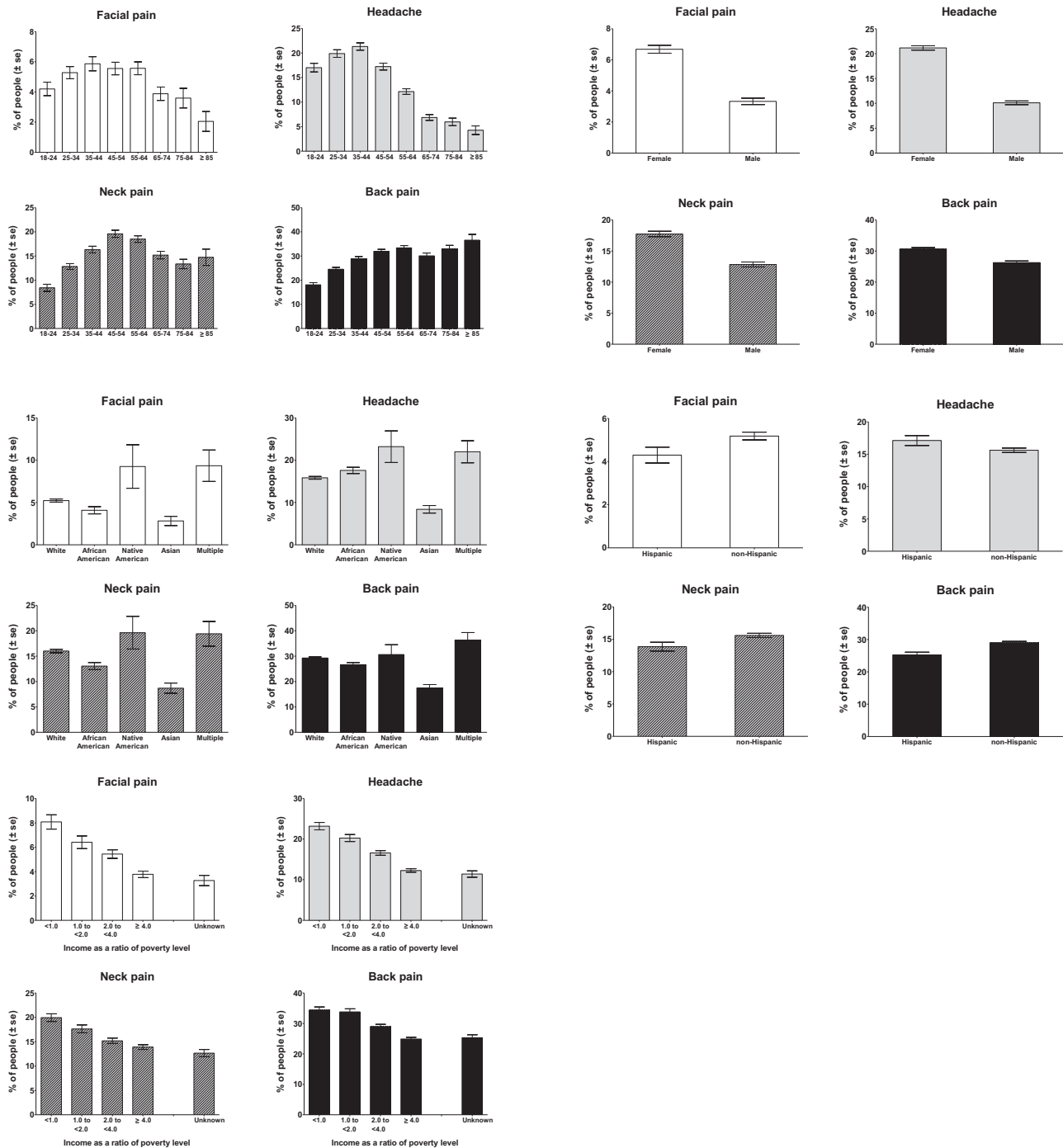


Figure 3. Sociodemographic distribution of 4 pain conditions in US adults, 2009. Source: the authors' analysis of the 2009 National Health Interview Survey.

Etiology and Mechanisms

There are 2 defining features of COPCs: 1) their etiologies are multifactorial, and 2) the clinical manifestations of COPCs are diverse and present as a mosaic of risk determinants for each COPC. Within each diagnostic category, there appear to be clusters of patients who appear to share characteristics with individuals in sub-groupings of the other diagnostic categories (ie, COPCs). We describe these characteristics (ie, putative multiple causes) as a mosaic to emphasize our expectation that

no single risk determinant is necessary or sufficient to cause 1 or more of the COPCs—just as multiple tiles are needed to depict the image in a mosaic. Understanding the interactions among multiple risk determinates, and/or their grouping into clusters, is required to better comprehend the etiological factors and mechanism(s) that contribute to the development and maintenance of COPCs.²³

COPCs vary significantly in clinical presentation. In addition to the cardinal symptom of pain, other common

Table 3. Association of Jaw/Face Pain and Other Pain Conditions, US Adults, 2009

No. of Comorbid Pain Conditions*	Population (Millions)	People with Jaw/Face Pain			
		People (Millions), N	Percentage of Population	Odds Ratio	95% CI†
0	118.4	1.3	1.1%	Referent	
1	57.1	2.0	3.6%	3.2	2.6, 4.0
2	29.8	3.0	10.1%	9.8	7.7, 12.4
3 or 4	21.9	5.1	23.4%	26.5	21.2, 33.0
Total	227.2	11.5	5.1%		

*1) Severe headache/migraine, 2) neck pain, 3) low back pain, and 4) 2 or more painful joints.

†95% Confidence limits for the odds ratio.

symptoms include fatigue, sleep impairment, problems with cognition, physical dysfunction, and disturbances in affect (eg, anxiety, anger, depression). Importantly, it is very likely that some groupings (ie, clusters) of patients share more clinical signs and symptoms across pain conditions than within a specific pain condition, consistent with the view that some overlap in etiological mechanisms underlies COPCs (Table 5). We and others have proposed that multiple genetic factors, when coupled with environmental exposures (eg, injury, infections, and physical and psychological stress), increase the susceptibility to highly prevalent COPCs by enhancing pain sensitivity and/or affecting psychological vulnerability (Fig 4).^{7,23}

Each COPC likely has common and also unique pathways or mechanisms of pathology.²³ Although the mechanisms that underlie most of these conditions are still poorly understood, COPCs have been associated with a state of pain amplification resulting from either peripheral and/or central mechanisms manifested as widespread hyperalgesia on the basis of quantitative sensory testing, with sensory and also affective perturbation^{9,12,41,72,107,117,134} (for review see Diatchenko et al²³). Importantly, there is substantial individual variability in the relative contribution of pain amplification and psychological phenotypes to COPCs.

Pain Amplification and COPCs

A few studies have sought to prospectively identify risk factors or risk determinants that are associated

with or mediate the onset and maintenance of COPCs. A well-established predictor of onset is the presence of another chronic pain condition, which is characterized by a state of pain amplification.¹¹⁸ Additionally, widespread pain is a risk indicator for dysfunction associated with painful TMD and for lack of response to treatment.⁸⁵ Several cross-sectional studies also suggest that a substantial percentage of individuals with an established COPC including TMD,^{68-71,91} IBS,^{58,117,120-122} FM,^{12,43,101,102} migraine headache,^{59,65,119} and vulvodynia^{66,83} are characterized by a state of pain amplification (for review see Yunus¹³⁰⁻¹³²). A review on this topic by Yunus¹³⁰ notes that a common feature inherent in a large percentage of patients with COPCs is enhanced pain sensitivity (Table 6). Whether pain amplification represents a risk determinant versus a consequence of COPCs remains a topic of debate. We previously reported that individuals who are more sensitive to noxious stimuli are significantly more likely to develop painful TMD than those who are less sensitive (risk ratio = 2.7).⁹⁶ However, more recent findings from a much larger cohort challenge this initial finding, and on the whole there is little evidence that sensitivity to experimental pain stimuli (thermal, mechanical, pressure) predict the onset or susceptibility to TMD and possibly other COPCs. However, it is clear that a state of increased pain sensitivity is augmented when TMD and perhaps other COPCs develop, suggesting that pain amplification may instead play a role in the maintenance (ie, chronification) rather than the onset (susceptibility) of COPCs.⁹⁹ These findings suggest that pain

Table 4. Association of Jaw/Face Pain and Health Conditions That Are Not Primarily Painful, US Adults, 2009

No. of Medical Conditions*	Population (Millions)	People with Jaw/Face Pain			
		No. of People (Millions)	Percentage of Population	Odds Ratio	95% CI†
0	102.0	2.8	2.7%	Referent	
1	60.4	2.8	4.6%	1.7	1.4, 2.1
2	34.7	2.3	6.8%	2.6	2.1, 3.2
3 or 4	30.1	3.6	12.0%	4.9	4.1, 5.9
Total	227.2	11.5	5.1%		

*Hypertension, heart disease, stroke, asthma, ulcer, cancer, diabetes, hay fever, sinusitis, chronic bronchitis, kidney disease, and liver disease.

†95% Confidence limits for the odds ratio.

Table 5. Published Estimates of Overlap Between Index Conditions and Other COPCs

INDEX CASE STATUS	COMORBIDITY (PERCENTAGE OVERLAP)				
	FM	IBS	TMD	CFS	VVD
FM		80 ³⁷	75 ⁸²	64 ²	NA
IBS	41 ¹³³		16 ⁵⁷	14 ⁵⁷	NA
TMD	24 ¹³³	64 ²		20 ²	NA
CFS	55 ¹³³	58 ³⁷	42 ⁶⁰		NA
VVD	23 ¹³³	25 ⁷⁵	20 ³⁹	8 ⁷⁵	

Abbreviations: COPC, chronic overlapping pain condition; FM, fibromyalgia; IBS, irritable bowel syndrome; TMD, temporomandibular disorders; CFS, chronic fatigue syndrome; VVD, vulvodynia; NA, not applicable.

amplification, and the associated processes that mediate pain transmission and modulation, represent key factors in maintaining COPCs.

Enhanced pain perception experienced by patients with COPCs may result from a dysregulation in peripheral systems, central systems, or both, that produce dynamic, time-dependent changes in the excitability and response characteristics of neuronal and glial cells, which may contribute to the central sensitization and the enhanced temporal summation (ie, wind-up) of nociceptive input observed in patients with COPCs. This dysregulation can also contribute to altered

mood, motor, autonomic, and neuroendocrine responses as well as altered pain perception (Fig 4).^{7,23} However, it should be noted that not all patients with an established COPC exhibit pain amplification.⁴¹ For example, although most TMD patients show enhanced sensitivity to ischemic pain,⁶⁹ approximately 25% of TMD patients show no change in ischemic pain perception relative to control subjects (Maixner and Fillingim, unpublished observation). Additionally, in a sample of interstitial cystitis patients, 81% exhibited widespread pain beyond the pelvic region (eg, suggestive of a more central and systemic disturbance), whereas only 19% appeared to have symptoms confined locally.⁷⁷ These findings are also observed for individuals presenting with chronic TMD and⁹⁷ strongly suggest that there are individual variations in the factors that contribute to pain sensitivity, which may create clusters of signs and symptoms observed in COPCs.^{41,90,106,107,111,126} These findings also suggest that there may be specific mechanisms operating within certain individuals that transform a localized pain condition into one that resembles a COPC. Therefore, for optimal classification of COPCs, it is important to characterize the heterogeneity of clinically measurable signs and symptoms in patients with COPCs, which will permit the patients with COPCs to be assigned to specific clusters or subgroups.

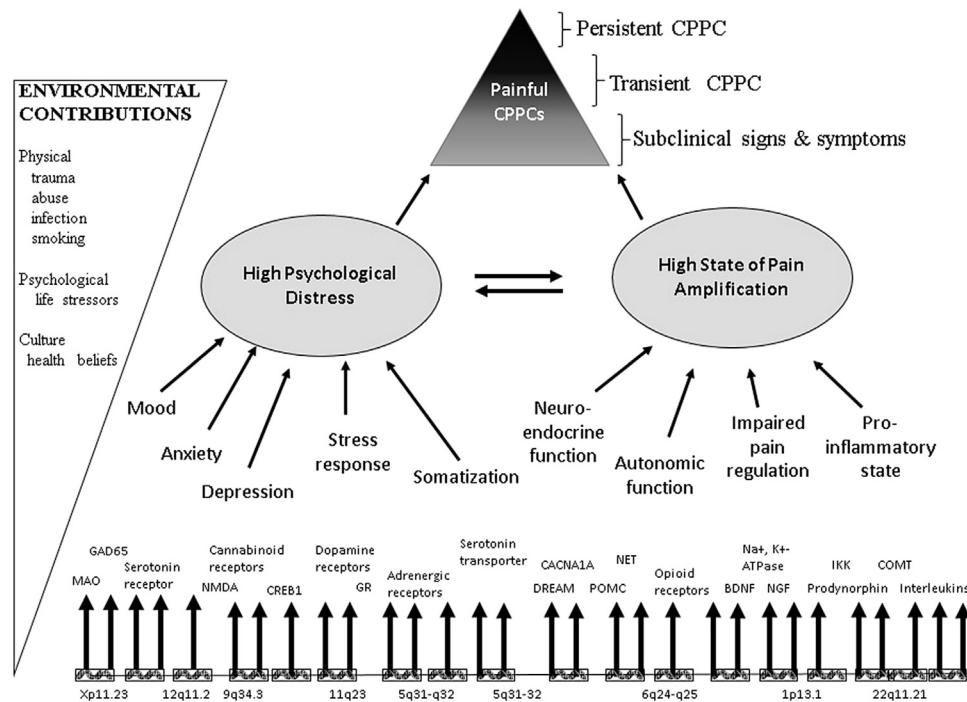


Figure 4. This model depicts likely determinants that contribute to the risk of onset and maintenance of common chronic overlapping pain conditions (COPCs). These factors are determined by genetic variability and environmental events that determine an individual's psychological profile and pain amplification status. These 2 primary domains are interactive and influence the risk of pain onset and persistence. Likely modifiers of the interaction between genetic and environmental factors include sex and ethnicity. Abbreviations: MAO, monoamine oxidase; GAD65, glutamate decarboxylase; NMDA, N-Methyl-D-aspartic acid; CREB1, CAMP responsive element binding protein 1; GR, glucocorticoid receptor; CACNA1, calcium channel, voltage-dependent, T type, alpha 1I subunit; POMC, proopiomelanocortin; NET, norepinephrine transporter; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; IKK, IκB kinase; COMT, catechol-O-methyl transferase.

Table 6. Number of Studies and Number of Patients Examined (Total N) Who Report an Increase in Pain Sensitivity Across Nociceptive Modalities and Across COPCs

STIMULUS	FM	CFS	IBS	TTH	Migraine	TMD	MPS/RSTPS	PD
Pressure (somatic)	15 (580)			4 (178)	3 (117)	2 (42)	9 (462)	1 (20)
Pressure (rectal)			26 (822)					
Heat (somatic)	12 (480)		2 (21)	1 (50)	3 (117)	3 (76)	3 (137)	2 (42)
Heat (rectal)			1 (46)					
Cold (somatic)	8 (255)		1 (33)		1 (41)		2 (184)	
Electric (cutaneous)	4 (61)		1 (12)				2 (36)	
Electric (intramuscular)	2 (41)	1 (23)					2 (36)	1 (10)
Electric (spinal reflex)	2 (107)		1 (14)	1 (40)			1 (27)	
Electric (rectal)			2 (21)					
Ischemic	1 (60)					2 (72)		
Hypertonic saline	2 (41)					1 (22)	1 (11)	
Auditory stimulus	1 (20)		1 (15)		1 (65)			

Abbreviations: COPC, chronic overlapping pain condition; FM, fibromyalgia syndrome; CFS, chronic fatigue syndrome; IBS, irritable bowel syndrome; TTH, tension type headache; TMD, temporomandibular disorders; MPS, myofascial pain syndrome; RSTPS, regional soft tissue pain syndrome; PD, primary dysmenorrhea.

Psychosocial Vulnerability and COPCs

Heightened psychosocial vulnerability represents another domain of risk factors for COPCs (Fig 4). Many patients with COPCs tend to have elevated depression, anxiety,^{107,111,114} and perceived stress⁹ relative to pain-free control subjects. A heightened burden of physical symptoms across multiple somatic systems is associated with more than a twofold increase in TMD incidence, decreased improvement in TMD facial pain after 5 years,⁸⁰ and increased pain after treatment.⁷⁴ High symptom burden has been associated with new onset of several COPCs, including TMD, widespread pain, and low back pain.^{4,45,64,72} Somatic symptom burden is also associated with the progression from acute to chronic TMD.³⁶ Additional psychosocial risk factors for development, persistence of COPCs, or both include depression, anxiety, psychosocial stress, and passive coping.^{55,64,76,96} These results suggest that multiple psychosocial factors, including somatic symptom burden, negative affect/mood, and environmental stress, independently or jointly contribute to the risk of onset and maintenance of COPCs and are therefore incorporated into the AAPT (see Edwards et al²⁸ and Turk et al¹¹⁰ in this issue of *The Journal of Pain*). However, like pain amplification, there are clusters of patients with COPCs who manifest mosaics of psychological processes and there will likely be large populations or clusters of patients with COPCs who display common and also unique psychological risk factors. There is a need to examine the heterogeneity of shared and unique psychological factors and clusters in large populations of patients with COPCs.

Genetic Variations Influencing Pain Amplification and Psychosocial Vulnerability

In the Etiology and Mechanisms section, we proposed that there are 2 major interactive domains that contribute to the vulnerability of developing and maintaining COPCs: pain amplification and psychosocial vulnerability (Fig 4). Each of these domains is influenced

by genetic variants that mediate the activity of physiological pathways that underlie pain amplification and cognitive and affective responses. Thus, individual polymorphic variations in genes coding for key proteins that regulate these pathways interact with environmental factors, such as physical or emotional stress, to produce a phenotype that is vulnerable to the development of COPCs. The commonality of pain amplification and psychosocial vulnerability in many patients with COPCs may shed light on common genetic processes responsible for the symptoms that cut across COPCs in otherwise anatomically localized pain conditions.

Clinical and experimental pain perception are influenced by genetic variants.^{22,24} The relative importance of genetic factors in human pain perception is becoming clearer with reported heritability for pain perception across several experimental modalities to range from 22% to 60%.^{78,79} Several recent studies have also established genetic associations with a variety of psychological traits and disorders that influence risk of developing COPCs. Twin studies show that 30% to 50% of individual variability in the risk of developing an anxiety disorder is due to genetic factors.⁴⁰ The heritability of unipolar depression is also remarkable, with estimates ranging from 40% to 70%.⁶² Moreover, normal variations in these psychological traits show substantial heritability.^{11,29,30,88} See [Supplementary Table 1](#) for a more comprehensive presentation of genetic variants that are associated with pain sensitivity and COPC conditions.

With advances in high-throughput genotyping methods, the number of genes associated with pain sensitivity has increased rapidly. A few examples of the genes associated with this domain include adrenergic receptor β_2 ,²¹ catechol-O-methyltransferase,^{24,25,135} dopamine receptor D4,⁵⁰ guanosine-5'-triphosphate cyclohydrolase 1,¹⁰⁵ μ -opioid receptor,^{34,93} and serotonin transporter.⁶³ These genes are prominent among those implicated as genetic risk factors for complex psychological disorders such as depression,^{21,32,87} anxiety,^{8,21} and stress response.^{5,6,116} Consistent with their role in pronociceptive traits, these genes have also been associated with 1 or more COPCs

(see [Supplementary Table 1](#) for a more comprehensive review).

Because it is highly likely that COPCs share common underlying pathophysiological mechanisms, it is expected that a set of functional genetic variants will be associated with comorbid COPCs and related signs and symptoms. For example, a common single-nucleotide polymorphism in codon 158 (val¹⁵⁸met) of the catechol-O-methyltransferase gene is associated with pain ratings, μ -opioid system responses,⁸⁴ TMD risk,²⁵ and FM development⁴⁴ as well as addiction, cognition, and common affective disorders.⁸¹ Common polymorphisms in the promoter of the serotonin transporter gene are associated with depression, stress-related suicidality,¹⁵ anxiety,⁴⁰ somatization, and TMD risk.⁴⁸ It is likely that there are several genes that exhibit such pleiotropic effects, which interact to contribute to specific quantitative phenotypic traits or factors that combine to form specific clusters ([Supplementary Table 1](#)).

However, a defining feature of COPCs is that it is very unlikely that a single genetic locus contains alleles that are necessary or sufficient to produce the complex set of signs and symptoms observed in COPCs. A substantial percentage of the variability observed with complex clinical phenotypes are best explained by genetic polymorphisms that are relatively common (ie, >10%) in the population, although the phenotypic penetrance of these common variants is frequently not very high.⁸⁹ Thus, the varied clinical phenotypes associated with COPCs are likely the result of interactions between many genetic variants of multiple genes that are responding to environmental exposures such as anatomic-specific injuries, physical and psychological stress, chemical exposures, infections, and a multitude of negative and positive life events. As a result, interactions among these distinct variants with a host of environmental exposures produce a wide range of clinical signs and symptoms so that not all patients show the same broad spectrum of abnormalities in pain amplification and affective vulnerability.

Because each individual patient with a COPC will experience a unique set of environmental exposures, and possess unique genetic antecedents to COPC vulnerability and manifestation, the most efficient approach to identify genetic markers for COPCs is to analyze the interactive effects of polymorphic variants of multiple functionally related genes. The complex interaction between these polymorphic variants will yield several unique subtypes of patients who are susceptible to a variety of COPCs. In addition, these multiple genetic pathways interact over time with environmental risk and resilience factors to influence the mosaic of signs and symptoms that define COPCs. A common and unifying feature of these temporally dynamic conditions is the expression of persistent pain as a primary symptom. The identification of complex interactions between environmental exposures and genetic susceptibility will enable the development of new algorithms and methods of diagnosing, classifying, and treating COPC patients. Although genotyping is not yet a common method

used for diagnostic classification of people with chronic pain, it seems likely that genetic testing or the assessment of downstream biological processes such as protein expression patterns will become an important component of the AAPT diagnostic process in the future, as additional evidence emerges regarding the molecular architecture of chronic pain conditions, including COPCs.

Classification and Diagnosis of COPCs

A challenge facing clinicians and researchers when considering the concept of COPCs is that although each of the diagnostic entities has its own case definition and classification criteria, there is still no consensus on exactly how these conditions overlap or how best to identify someone as a COPC “case.” As noted previously (Epidemiology of COPCs) many individuals with 1 condition also tend to meet diagnostic criteria for other conditions—but not everyone. This observation raises the question of whether 1) each singular condition is a primary problem with some people exhibiting a secondary disorder (ie, COPC) that appears to overlap with the primary condition(s), or 2) all of the conditions share a common underlying mechanism (ie, COPC), and severity varies along a continuum with some individuals displaying only a singular manifestation whereas more severe cases exhibit multiple conditions dictated by genetic susceptibility and the nature of specific environmental exposures. As noted previously, the degree to which COPCs share common and unique risk vectors that results in clusters or groupings of COPCs is also an open question.

Currently, the classification criteria for each condition vary greatly in the rigor by which they were established, with some including behavioral factors, some biomarkers, and others self-reported symptoms. In addition, the evidence supporting the existing diagnostic criteria varies notably across pain conditions. [Table 1](#) shows the currently available options for classifying each condition.

Although each condition appears to have some unique anatomic pathophysiology, there is often shared symptomatology (eg, widespread pain), epidemiology (eg, higher female prevalence), and putative shared underlying mechanisms (eg, pain amplification, psychosocial, genetic) that suggest these conditions are related. The challenge for clinicians has been how to classify individual patients with the goal of identifying the most effective treatment for a COPC patient on the basis of symptoms and mechanisms. All too often, treatment is comprised solely of medications that target only pain, to the exclusion of the many other signs and symptoms that comprise the mosaic pattern of COPCs. To help identify subgroups of patients that share common pathways of vulnerability, and who may respond to specific treatments, there is a need for diagnostic and classification schemes on the basis of biopsychosocial factors.²² The multidimensional AAPT framework represents a step in this direction.³³ To fully operationalize this type of multidimensional classification, comprehensive assessment is required. Pain assessment would include

traditional measures of clinical pain intensity but would also include pain location, pain quality, pain distribution (eg, widespreadness), and temporal patterns or characteristics (see Fillingim et al, in this issue of *The Journal of Pain*). As discussed elsewhere in this issue of *The Journal of Pain*, by Edwards et al²⁸ and Turk et al,¹¹⁰ the comorbid symptoms that accompany many of the COPCs must also be assessed, including: fatigue, polysomatic illness burden, nonrestorative sleep, and dyscognition (eg, poor memory, cognitive clarity, and attention). Because chronic pain is heavily influenced by affective factors, assessment of anxiety, dysphoria/depression, anger, stress, trauma history, and personality should be included to identify subpopulations of COPC patients who will respond to affect-specific pharmacological and nonpharmacological therapies. Beliefs and attitudes about pain also have strong relationships to functional status and chronification.^{13,112} Such cognitive factors can include catastrophizing, locus of control, self-efficacy, expectancies, coping resources, and resilience. Behavioral responses to COPCs include functional status, fear avoidance, interference from pain and disability, and finally interpersonal responses, which often occur in social contexts can influence pain (eg, evaluation of culture, family, work, and medical support) as discussed by Turk et al¹¹⁰ in this issue of *The Journal of Pain*.

Although assessing all of these domains is not practical clinically, screening methods are needed that permit the identification of patients requiring more intensive treatments. Computer adaptive testing approaches also can be implemented, which greatly reduce respondent burden.^{103,104} In addition, more comprehensive approaches can be useful in phenotyping and mechanistic-based research. Work from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has helped to identify the primary domains that should be used as outcome measures (eg, end points) in the context of clinical trials of pain treatments, which include: 1) pain intensity, 2) physical functioning, 3) emotional functioning, 4) overall improvement/well-being, and (5) side effects.^{108,109} A similarly multidimensional approach is important for classification of chronic pain conditions. An even smaller subset may be possible when the purpose of assessment is disease or symptom monitoring over time. However, a broader set of biopsychosocial variables, including genetic factors, need to be assessed to determine the mechanistic factors that are either unique or shared by COPCs.

Despite our ability to assess multiple facets relevant to COPCs, treatment of COPCs and chronic pain more generally, remains challenging. Current interventions retain a focus on sensory aspects of pain despite the knowledge that chronic pain is heavily influenced by biopsychosocial factors.^{7,56,73} Evidence-based approaches suggest that combinations of traditional and centrally acting medication produce modest benefits for many COPCs¹⁶ and that combining medications with nonpharmacological interventions can produce even greater benefits in pain relief and functional status for many of the COPCs. For example, psychological interventions show significant

benefits in individuals with FM,¹²⁵ IBS,⁶¹ chronic lower back pain,⁵¹ and headache.²⁷ However, clinical pain reductions with these interventions may only help a subset and overall can appear to be modest.^{3,124,125} Additional nonmedical interventions, such as exercise, also can benefit individuals with COPCs.^{14,100}

Despite some positive evidence for combination therapy for COPCs,¹⁶ clinical outcomes remain suboptimal and additional research and stratification methods are needed. This may be in part attributable to the failure to appropriately incorporate COPCs into the design and conduct of most clinical trials. Indeed, clinical trials for pain treatments typically target a specific pain condition, and the presence of other pain conditions is often an exclusion criterion.^{67,94} Thus, individuals with COPCs are significantly under-represented in clinical trials, resulting in a dearth of information regarding safe and effective therapies for patients with these common conditions.

Several steps can be taken to address this situation. First, clinical trials should incorporate rather than exclude COPCs into their designs. The most basic approach would be for a clinical trial of a treatment for a specific COPC (eg, low back pain) to allow inclusion of people with additional COPCs, collecting detailed information on the presence and severity of other conditions. An alternative approach would be to conduct a trial to determine the efficacy of a treatment for COPCs rather than for specific individual pain conditions. This would require an agreed upon case classification for COPCs as well as systematic collection of data about each of the pain conditions a patient endorses. If COPCs are driven by common underlying mechanisms, treatments designed to address those mechanisms should be effective for COPCs broadly defined.

Regardless of how future trials account for COPCs, another important step will be to collect more comprehensive biopsychosocial and molecular data, across multiple domains, to allow investigators to identify subgroups that reflect potentially distinct pathophysiologic mechanisms (Fig 4). Broad-based information regarding clinical features, pain amplification, and psychosocial functioning can be subjected to sophisticated statistical approaches (eg, cluster analysis, latent class analysis) to permit identification of phenotypic profiles. These phenotypic data can then be combined with genetic and other biomarker data to characterize the biological mechanisms contributing to the empirically defined subgroups. Stratified analysis can then be performed to identify subgroups that are particularly responsive (or nonresponsive) to treatment. Future research will need to focus on which combinations of assessed domains (eg, sensory, cognitive, affective, behavioral) and procedures provide the most rational routes into the subclassification and the identification of treatment targets for specific strata or clusters of COPCs, with the goal of providing meaningful pain relief, restoration of function, and improved quality of life. Historically a singular focus on reduction in anatomically specific clinical pain has proven to be inadequate for meaningful treatment of COPCs.

Recommendations and Future Directions

1. Develop an empirically validated, evidence-based, and mechanistically-driven case classification for COPCs.
2. Design clinical trials that incorporate rather than exclude COPCs to promote identification of safe and effective therapies for patients with these conditions.
3. Develop phenotyping assessment procedures that can be readily operationalized that permit the subgrouping of patients with COPCs on the basis of pathophysiological mechanisms. This could lead to new nonanatomically based diagnostic taxonomies as well as the identification of subgroups for whom specific therapies are highly efficacious.
4. Conduct research on subgroups of COPCs to identify underlying molecular mechanisms and targets

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5. Examine interventions that focus on the amelioration of vulnerability factors and engagement of resilience factors in subgroups of COPCs.

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Supplementary Data

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