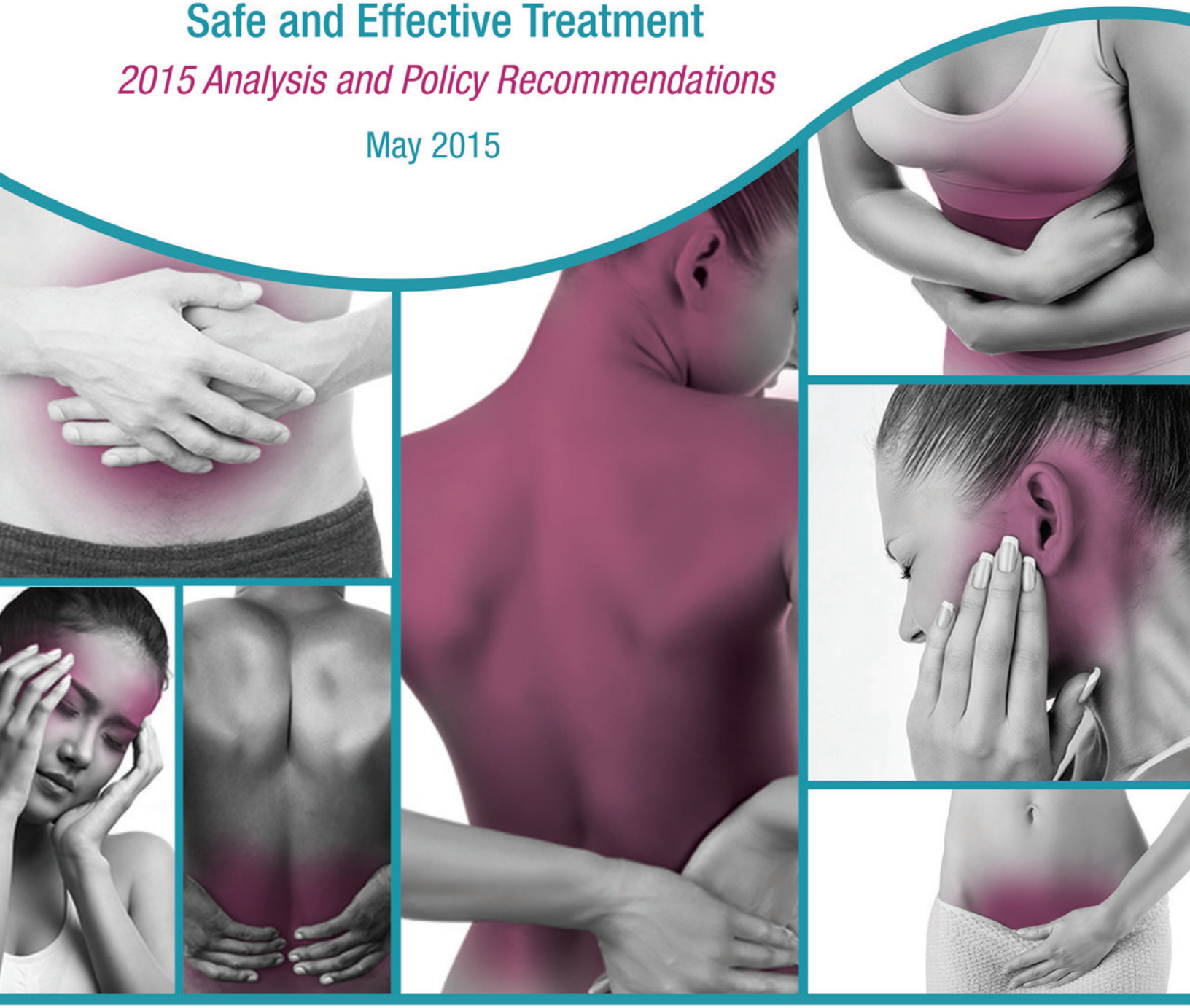
Impact of Chronic Overlapping Pain Conditions on Public Health and the Urgent Need for Safe and Effective Treatment

2015 Analysis and Policy Recommendations

May 2015



Produced by

CHRONIC PAIN Research Alliance

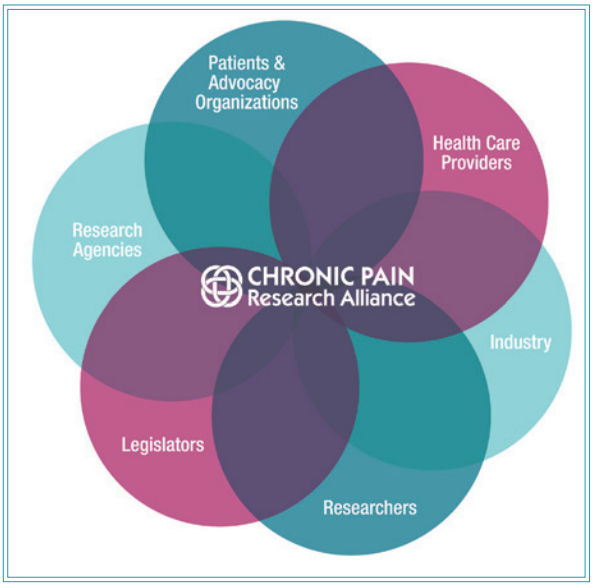
Advancing Research – Changing Lives

About the Chronic Pain Research Alliance

The Chronic Pain Research Alliance (CPRA) exists to provide a voice for the millions of people suffering with multiple pain conditions, termed *Chronic Overlapping Pain Conditions (COPCs)*. These conditions come at a high cost – to the individuals affected by them, their loved ones and to our health care system and society at large. Misdiagnosis is all too common, coordinated medical care is lacking, and safe and effective treatments are sparse.

Why is this? A major reason is that only **$1.06 per affected person** is invested in researching these conditions by the federal government.

We are working tirelessly to change that!



For meaningful change to occur in the lives of those suffering from COPCs, CPRA understands that all invested stakeholders must work together. This includes patients affected by COPCs and their loved ones, clinicians who care for them, scientists researching these conditions, companies working to develop better and more effective treatments, federal and private research agencies who support research studies, advocacy organizations working to improve the lives of people with these conditions and legislators who affect change through public policy.

With the ultimate goal of advancing timely diagnoses and effective evidence-based medical management for individuals affected by COPCs, the CPRA works with invested stakeholders to:

1 - Promote high-quality research on chronic overlapping pain conditions
2 - Translate research findings into information for patients and educational training programs for clinicians
3 - Drive the development of safe and effective treatments for these conditions

CPRA's Vision for the Future

With the advancement of initiatives called for by the CPRA, we envision a future where individuals with COPCs will receive a timely and accurate diagnosis, following by high-quality, comprehensive medical care that is informed by the latest and most rigorous scientific evidence.

In the process, these goals will be attained:

- ✓ Increased federal and private investment in COPCs research that is coordinated, standardized and collaborative
- ✓ Informed and educated health care professionals
- ✓ Informed and empowered patients
- ✓ Development of safe and effective therapies specific to COPCs
- ✓ Maximized taxpayer dollars and decreased costs

To learn more, please visit: www.ChronicPainResearch.org.

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CPRA Scientific Advisory Council

Section I: Executive Summary

The Institute of Medicine's (IOM) historic 2011 report, *Relieving Pain in America*, documented the profound cumulative impact of chronic pain on our nation, finding that four in ten American adults live with chronic pain disorders, with annual costs exceeding $500 billion. The IOM report noted the increasing recognition and importance of a cluster of prevalent pain conditions that frequently co-occur and either solely or predominantly affect women. These disorders, recently termed by the U.S. Congress and National Institutes of Health as *Chronic Overlapping Pain Conditions* (COPCs), include: vulvodynia, temporomandibular disorders, myalgic encephalomyelitis/chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, fibromyalgia, endometriosis, chronic tension-type and migraine headache and chronic low back pain.

"The magnitude of the pain suffered by individuals and the associated costs constitute a crisis for America, both human and economic. Addressing the nation's enormous burden of pain will require a cultural transformation in the way pain is understood, assessed, and treated [and] represents a moral and national imperative."
~ Relieving Pain in America, Institute of Medicine, 2011

A growing number of studies – mostly conducted in clinic-based populations – demonstrate variable rates of overlap among COPCs, as well as increased risk of developing a new, different COPC as the number of pain conditions a person has increases. Large, long-term prospective studies that include people from the general population are beginning to yield rigorous epidemiological data on rates of co-occurrence and relative risk, as well as the temporal relationship among COPCs. Mounting publications further substantiate that these conditions share common underlying disease mechanisms, mainly in the immune, neural and endocrine systems. Cumulatively, evidence suggests that the delay in accurate diagnosis and effective treatment commonly experienced by individuals with COPCs can have serious consequences, including worsening of both site-specific and body-wide symptoms, which in turn, makes COPCs more difficult to effectively treat. A vicious cycle ensues, leading to poorer health outcomes, diminished quality of life and increased disability. The toll extends far beyond the affected and their families, substantially impacting the health, workforce and productivity of our nation as a whole.

"I wish someone would have had the insight to see how these conditions are interconnected, and had been able to intervene sooner so that I didn't have to suffer as much…and those around me didn't have to suffer."
~ Paula, COPCs patient

In spite of this, the federal investment in researching these disorders is woefully inadequate – averaging just $1.06 per affected individual in Fiscal Year 2014, down eight percent from the prior year. Research and clinical efforts to date have lacked coordination, efficiency and efficacy. As a result, evidence-based treatment options are not only few, but inadequate. Only a handful of FDA-approved therapies exist for half of these conditions, only two of which have been approved in the last five years. None are indicated for more than one COPC, although several are used off-label to treat most of these disorders. The resultant situation is that COPCs sufferers and their clinicians must use trial-and-error methods selected from a myriad of treatments, most with unknown safety and efficacy data (especially when combined), until they identify a combination that brings some relief. Numerous systematic reviews describe the poor state of evidence on the efficacy of treatments for COPCs.

Given their widespread prevalence and financial toll, significant rates of overlap, similar symptom presentation, common mechanisms of disease and appreciable unmet treatment demand, there is both an urgent need and tremendous opportunity to advance a comprehensive, rigorous and coordinated research and development effort for COPCs. Priorities include furthering scientific understanding of common underlying disease mechanisms, as well as developing and testing safe and effective treatments that can be used across COPCs. To date, the National Institutes of Health has funded three large, multi-site, national research collaborations to advance a comprehensive scientific approach to understanding the epidemiology and pathophysiology of COPCs, each of which includes a different combination of some, but not all of the disorders. These studies are beginning to yield extremely useful information; however, in order to truly translate scientific discoveries into meaningful clinical change for individuals with COPCs, what is needed is a coordinated, collaborative initiative that spans the continuum of basic, translational and clinical research and

Table 1. Themes for Chronic Overlapping Pain Conditions (COPCs) – Past and Future

This table summarizes the old (past) and new (future) conceptualization of important themes for COPCs, described throughout this report.

	Past	Future
Scientific Understanding	Each condition is distinct with its own disease mechanisms at the painful body site	Altered neural, immune and endocrine mechanisms are common across disorders
Diagnosis	Individual disorders with separate diagnostic labels that can co-exist	One universal disorder with multiple presentations (e.g., subgroups/phenotypes)
Medical Management	All pain is due to peripheral damage or inflammation in specific body areas and will respond to treatments used for acute pain (e.g., interventions, surgery, opioids)	Some pain conditions are ultimately due to dysregulation of the neural, immune and endocrine systems, and will not respond favorably to treatments for acute pain, which may worsen pain or cause harm
	Medical care is fragmented by disparate specialists, typically determined by physical location of pain (e.g., rheumatology for fibromyalgia, urology for interstitial cystitis)	Patient-centered medical home with team-based interdisciplinary approach to treatment
	Palliative treatment that only abates symptoms to various degrees	Selection of treatment regimen is guided by individual's pathophysiology/underlying mechanisms of disease (e.g., personalized medicine)
	Treatment is trial-and-error and draws upon findings from better researched disorders	Treatment is based on scientific evidence, showing proven efficacy in specific mechanism-based subtypes
	Treatment of most painful symptom or body part	Recognition that multiple domains of health and quality of life are affected, and that integrated care is guided by the development of an individualized treatment plan of all affected domains and contributing factors (e.g., sleep, mood, pain interference)
	Fee-for-service model often does not benefit patients and can contribute to worsening of the patient's health	Quality- and performance-based reimbursement focused on effectiveness and quality of care received
Research Efforts	Disorders are researched separately by diagnostic label or body site, with similar lines of study duplicated across conditions (e.g., brain imaging, genetics, sensory testing)	Disorders are researched collectively to assess common underlying mechanisms, as well as unique features of each condition in different patient subgroups/phenotypes
Translation of Evidence	Evidence not widely disseminated or translated into improved clinical tools or medical care	Heavy focus on translation of scientific findings into improved tools and clinical care
Systemic Federal Research Agency Issues	Federal research agencies remain structured such that conditions are researched in isolation or silo, and efforts to approve therapies are fragmented and not to the patient's benefit	Patient-centered research focus, where federal research agencies work collaboratively to address patient needs and cross-agency mission, with the goal of translating scientific discoveries into therapeutic solutions

includes all necessary stakeholders – academia, industry, government agencies, service and reimbursement sectors, clinical care, and advocacy and philanthropic organizations.

This report contains vital recommendations for federal, private and corporate entities, which if developed and implemented, would achieve this goal and would also impart long-term cost savings to our health care system and nation as a whole. CPRA's vision for the future is to generate urgently needed diagnostic and treatment guidelines informed by a comprehensive COPCs research initiative. These guidelines would be used to optimally educate and train health care providers, so that they are equipped to provide quality evidence-based medical care to those suffering from these life-altering disorders–leading to a significant improvement in their health and quality of life.

"Research holds possibilities that help me fight through another day of pain, giving me hope for a better future for myself and others who are suffering."
~ COPCs patient

Section II: Background

On March 23, 2010, President Barack Obama signed into law *The Patient Protection and Affordable Care Act*. Included were several pain-related provisions, one of which directed the Secretary of Health and Human Services to enter into an agreement with the Institute of Medicine (IOM) to convene the first IOM conference on pain in America, as well as to submit a report to the U.S. Congress on its findings.[1] In June 2011, the IOM published the resultant report, *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Research and Education*, which for the first time documented the profound cumulative impact of chronic pain on our nation, demonstrating that over 100 million Americans spend each day in chronic pain, at a cost of over $500 billion in health care and lost productivity each year.[2 3]

Major findings of this historic report include:

- "The magnitude of the pain suffered by individuals and the associated cost constitute a crisis for America, both human and economic."
- "Effective pain management is a moral imperative, a professional responsibility and the duty of people in the healing professions."
- "Although pain is known to be prevalent across society, reliable data are lacking on the full scope of the problem, especially among those currently underdiagnosed and untreated."
- "Meeting these challenges [imposed by chronic pain] will require a cultural transformation in the way that pain is perceived and managed on both the personal and societal levels." [4]

The IOM report noted the increasing recognition and importance of chronic pain disorders that frequently co-occur and either solely or predominantly affect women, referencing the Chronic Pain Research Alliance's (CPRA) May 2010 White Paper, *Chronic Pain in Women: Neglect, Dismissal and Discrimination*.[5 6] The CPRA's landmark report, for the first time, documented the mounting scientific evidence substantiating the co-occurrence of just six disorders – vulvodynia, temporomandibular disorders, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, fibromyalgia and endometriosis – which together may affect over 50 million people and consume upwards of $80 billion annually in direct and indirect health care expenses. These billions of dollars buy sufferers very little real or lasting relief, as patients are forced to endure repeated medical visits and undergo multiple invasive interventions that may be ineffective or worsen their condition. In 2010, the National Institutes of Health (NIH) invested only $65 million in research into these six conditions – just about two-tenths of one percent of its total budget. That is an average of just $1.33 for every affected person and represents less than one-tenth of one percent of the annual estimated cost of these conditions.

"It is very difficult to cope – physically, financially and emotionally – because you are trying to find solutions to a problem that nobody seems to have the exact solution to."
~ Joy, COPCs patient

Further, the document noted that due to the scant funding allocated to researching these conditions, clinicians do not have sufficient data needed to develop evidence-based diagnostic and treatment protocols. The financial burden

associated with the "trial-and-error" treatment of these conditions falls upon those affected, their loved ones and society as a whole. Sufferers' debilitation and disability prevent a significant percentage from fully utilizing their talents and skills to contribute optimally to our society and economy.

Since the release of the 2011 IOM Report, these encouraging steps have been taken:

- In fall 2011, the National Institutes of Health established a Trans-NIH Chronic Overlapping Pain Conditions Working Group, which includes 12 NIH Institutes/Centers and whose purpose is to assure coordination of research efforts across the NIH on chronic overlapping pain conditions (COPCs). [7]

- In September 2011, co-sponsored by the NIH, The TMJ Association focused its Sixth Scientific Meeting on COPCs titled, *Comorbid Chronic Pain Conditions – Mechanisms, Diagnosis and Treatments*. [8]

- In February 2012, the U.S. Senate held the first hearing on chronic pain, *Pain in America: Exploring Challenges to Relief*, which included the testimony of a CPRA Co-Founder and Scientific Advisory Council members on COPCs. [9]

- In 2012, the NIH designated the National Institute of Neurological Disorders and Stroke as the lead institute for coordinating pain research efforts across the NIH. [10]

- In spring 2012, with the goal of improving how medical professionals are taught about pain, the NIH Pain Consortium designated 12 health professional schools as Centers of Excellence in Pain Education (CoEPEs), to act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing and pharmacy schools. [11]

- In August 2012, the NIH held the first scientific meeting on COPCs, *A Workshop on Chronic Overlapping Pain Conditions*, and subsequently published the resultant research recommendations. [12]

- In late 2012, the NIH instituted the Office of Pain Policy (OPP) within the National Institute of Neurological Disorders and Stroke, whose purpose is to support the activities of the NIH Pain Consortium and the Interagency Pain Research Coordinating Committee (IPRCC).

- In October 2012, the Secretary of Health and Human Services (HHS) charged the IPRCC with the responsibility of convening the National Pain Strategy Task Force, whose purpose is to develop a strategic operational plan for IOM Report Recommendation 2.2 - to advance pain prevention, care, education and research; facilitated through the NIH OPP, the Task Force completed the plan in October 2014, and it is expected to be published by HHS in mid-late 2015. [13]

- In June 2014, NIH released the first federal research Funding Opportunity Announcement on COPCs, co-sponsored by six NIH Institutes, Centers and Offices. [14]

- In September 2014, co-sponsored by the NIH, The TMJ Association focused its Seventh Scientific Meeting on COPCs titled, *Genetic and Epigenetic Basis of Temporomandibular Disorders and Related Chronic Overlapping Conditions*. [15]

- In September 2014, with the goal of maximizing the federal research investment in COPCs, the NIH convened the second federal scientific meeting of COPCs investigators, specifically to develop a Common Data Elements program and federal data-sharing repository. [16]

- In January 2015, the NIH Office of Pain Policy developed a Working Group to guide the process of developing a Common Data Elements program and data-sharing repository for COPCs.

Although these initiatives lay the foundation for much-needed reform, work in this area is in its infancy and a significant effort requiring a more robust investment is required. As detailed in this report, what has resulted from the longtime neglect of COPCs and delay in researching them is a poor understanding of their underlying disease mechanisms – both common and unique – and minimal-to-no translation of scientific findings into the development of safe and effective FDA-approved treatments for the millions of Americans suffering from COPCs. This report also summarizes promising new research partnerships focused on COPCs and provides a summary of research tools that can be used by the medical-scientific community studying these disorders. Further, it presents imperative recommendations for how research on COPCs should be advanced and expanded in a coordinated fashion to efficiently and effectively maximize the federal research investment, leading to the translation of scientific findings into improved health and quality of life for those suffering from chronic overlapping pain conditions.

Section III: Prevalence, Burden of Illness and Societal Impact of Chronic Overlapping Pain Conditions

Mounting scientific evidence demonstrates significant rates of overlap among a cluster of prevalent poorly understood pain disorders that solely or predominantly affect women. Although various terms have been used in prior years to describe the clinical state of overlap among these conditions (e.g., central sensitivity syndromes, complex persistent pain conditions), the U.S. Congress and National Institutes of Health recently termed them *Chronic Overlapping Pain Conditions* (COPCs). (See Figure 1.)

They include:

- Vulvodynia
- Temporomandibular Disorders
- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
- Irritable Bowel Syndrome
- Interstitial Cystitis/Painful Bladder Syndrome
- Fibromyalgia
- Endometriosis
- Chronic Tension-Type Headache
- Chronic Migraine Headache
- Chronic Low Back Pain

In a certain percentage of people with these conditions, the associated pain can be attributed to a pathophysiological process in the affected peripheral tissue, such as inflammation or lesions. However, in a significant percentage of affected individuals, no "end-organ" pathology is found; rather, patients demonstrate common abnormalities in neural, immune and endocrine function. (See Section VI on page 22 for a detailed summary on common underlying disease mechanisms.) A growing number of studies (mostly conducted in clinic-based populations) demonstrate variable rates of overlap among COPCs, as well as increased risk of developing a new, different COPC as the number of pain conditions a person has increases.[17-57] (See Figure 2 and Table 2.) Large, long-term prospective studies, which include people from the general population, and specialized phenotyping studies are beginning to yield rigorous epidemiological data on rates of co-occurrence and relative risk, as well as the temporal relationship among COPCs. [58-65]

Figure 1. Venn Diagram of Chronic Overlapping Pain Conditions

The complexity of overlap among COPCs is demonstrated in this figure. Any combination of conditions is possible. Some people may develop two disorders – either simultaneously or over the course of their lives – while others may develop three or more.

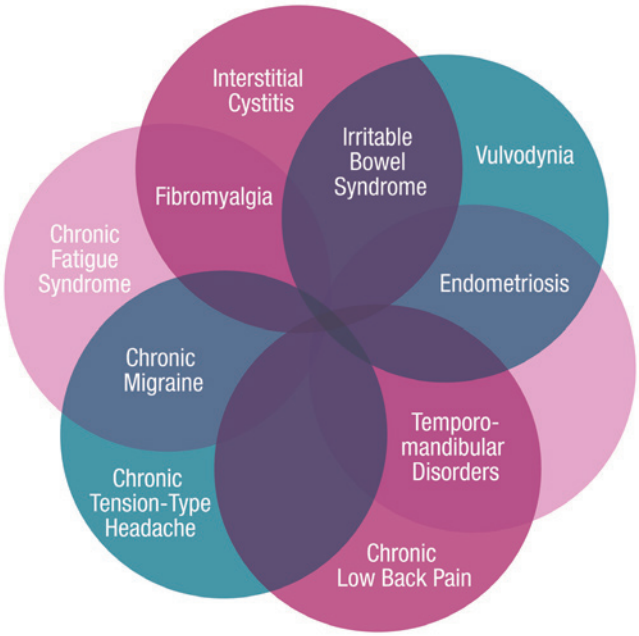


Figure 2. Number of Medical Journal Articles Published on Various Combinations of COPCs Increases Five-Fold Between 1995 and 2014

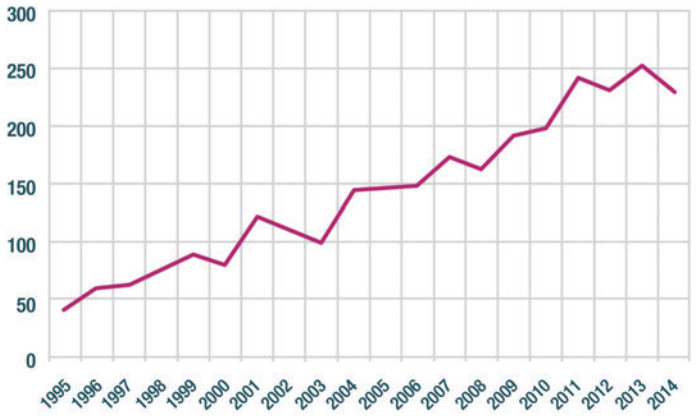


Table 2. Number of Medical Journal Articles Published on Various Combinations of COPCs Between January 2013 and December 2014

A total of 804 (482 non-duplicate) medical journal articles were published in this time period. Most common were publications on the relationship between ME/CFS and FM (128 articles), IBS and FM (74 articles), migraine and TMD (66 articles) and ME/CFS and IBS (58 articles).

	ENDO	FM	IBS	IC/PBS	Migraine	cTTH	Vulvodynia	cLBP	TMD
ME/CFS	9	128	58	23	15	2	6	3	6
ENDO		13	16	18	8	1	10	8	2
FM			74	32	41	3	15	38	25
IBS				33	39	1	9	6	9
IC/PBS					7	0	10	1	4
Migraine						--	0	23	66
cTTH							0	5	20
Vulvodynia								1	4
cLBP									12
TMD									

Note: ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome; ENDO: endometriosis; FM: fibromyalgia; IBS: irritable bowel syndrome; IC/PBS: interstitial cystitis/painful bladder syndrome; cTTH: chronic tension type headache; cLBP: chronic low back pain; TMD: temporomandibular disorders

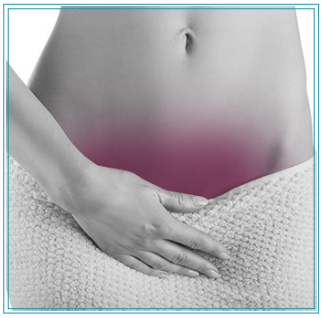
Cumulatively, evidence suggests that the delay in accurate diagnosis and effective treatment commonly experienced by individuals with COPCs can have serious consequences, including worsening of both site-specific and body-wide symptoms, which in turn, makes COPCs more difficult to effectively treat; a vicious cycle ensues, leading to poorer health outcomes, diminished quality of life and increased disability. [66-106]
A wealth of studies demonstrate the profound impact these stigmatizing disorders have on all aspects of health and quality of life, putting patients at increased risk of suicide, with a typical pattern as is pictorially described in Figure 3.[107-124]
The toll extends far beyond the affected and their families, substantially impacting the health, workforce and productivity of our nation as a whole.

"You get to the point where you say, 'I have to help myself. I have to be a fighter. I have to really find strategies to help take care of myself.' "
~ Paula, COPCs patient

"[Our daughter] tried to be upbeat when she communicated with her friends and relatives, but we knew how miserable she was. We tried to remain positive and hopeful for her."
~ Parents of COPCs patient

Figure 3. Typical Pattern and Profound Quality of Life Impact Experienced by Those with COPCs [107]

This figure depicts a typical pattern experienced by individuals with COPCs. Because our health system is fragmented by medical specialties, this cycle is further complicated as the affected individual: develops additional conditions; seeks care from different medical specialists (e.g., urology for bladder pain, rheumatology for fibromyalgia, gynecology for vulvodynia); receives multiple treatment recommendations; deals with disagreement among providers; lacks a primary clinician to coordinate medical care; and experiences further stigma and invalidation, poorer health and quality of life outcomes and increased levels of disability.



Vulvodynia

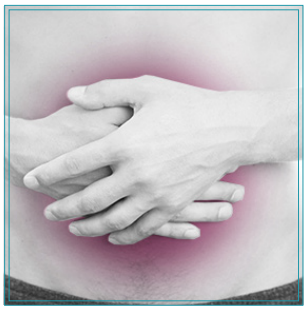
Vulvodynia is chronic pain in the vulva – the anatomical area surrounding the vaginal opening – without an identifiable cause.[125] The most common subtypes are generalized vulvodynia and provoked vestibulodynia (previously known as vulvar vestibulitis syndrome).[126] The most common symptom is burning; however, the pain has also been described as stabbing, raw, stinging and knife-like. A recent NIH-funded population-based research study demonstrated that the condition is widely prevalent, in that one in four women of all ages and ethnicities will be affected at some point in their lives.[127] Several independent NIH-funded population-based studies that include a clinical confirmation component demonstrate a point prevalence of three to seven percent in reproductive-aged women.[128 129] A recent study of adolescent girls suggests it may be quite prevalent among young women as well.[130] Vulvodynia is not limited to a particular age group; however, a major study of adult women found that the incidence of symptom onset is highest between the ages of 18 and 25.[131] Using prevalence estimates of three to seven percent, Xie and colleagues demonstrated an economic impact of $31–$72 billion, with 70 percent representing direct health care costs.[132]

Temporomandibular Disorders (TMD)

Temporomandibular Disorders are characterized by pain in the jaw joint and surrounding muscle/tissues and jaw movement limitations. One or both joints may be involved and depending on the severity, affect a person's ability to speak, chew, swallow, make facial expressions and even breathe. Approximately 35 million Americans suffer from TMD and the prevalence is higher in women than in men, as 90 percent of patients seeking treatment are women of childbearing age; age of symptom onset ranges from teens to 50.[133-135] A study sponsored by the Agency for Healthcare Research and Quality demonstrated an economic impact of $32 billion annually.[136]

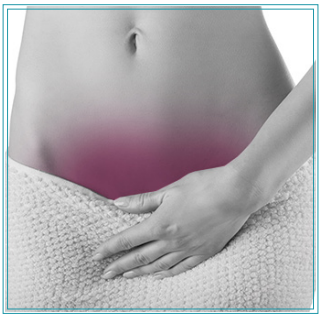
Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS)

The U.S. Food and Drug Administration describes ME/CFS as, *"a complex, debilitating disease characterized by profound fatigue lasting for six or more consecutive months that is not improved by bed rest and that may be worsened by physical or mental activity."* [137] The nature and severity of symptoms vary from person to person; however, many body systems are known to be affected, with ME/CFS patients experiencing severe muscle and joint pain, cognitive impairment, unrefreshing sleep and a worsening of symptoms with mental or physical exertion.[138] Despite the fact that the cause of ME/CFS is not known, these chronic and debilitating symptoms are known to increase long-term disability and premature death.[139] According to the Centers for Disease Control and Prevention, between one and four million people in the United States are afflicted with ME/CFS.[140] The disease may occur with sudden onset, such as following an infection, or it may develop gradually. The onset of ME/CFS symptoms occurs in two distinct age ranges; the first peak occurs between the ages of 10–19 years and the second peak between the ages of 30–39.[141] Although more common in women, ME/CFS also affects men, as well as people of all racial, age, and socioeconomic groups.[142] The economic impact of ME/CFS is reported to be $37 billion in medical costs and lost productivity.[143]



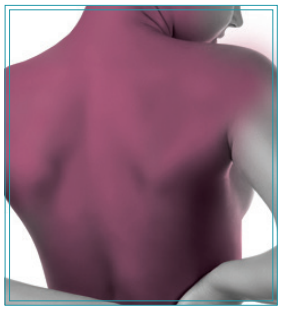
Irritable Bowel Syndrome (IBS)

Irritable Bowel Syndrome is a group of symptoms – including pain or discomfort in the abdomen and changes in bowel movement patterns – that occur together. It is referred to as a 'functional gastrointestinal disorder,' because abnormalities in the gastrointestinal tract are experienced without evidence of damage due to a disease. There are four subtypes of IBS: with diarrhea, with constipation, mixed and unknown. In the U.S., the prevalence of all types of irritable bowel syndrome is estimated to be 14 percent of the general population.[144] Women are approximately two times as likely to suffer from IBS compared to men, and adults under the age of 45 years are more likely than older adults to be affected. A 2013 systematic review suggests that the U.S. direct and indirect costs of IBS may be as high as $380 billion.[145]



Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS)

Interstitial cystitis (IC) – also known as painful bladder syndrome and bladder pain syndrome – is characterized by pain, pressure or discomfort of the bladder in the absence of infection or other pathology. Sufferers also typically experience urinary frequency and urgency and may have pain during or after intercourse. Based on the RICE and BACH studies, between three to eight million women and one to four million men suffer from IC.[146-148] The average age of symptom onset is 40 years.[149] A 2011 study found the U.S. direct costs of IC to be $22 billion.[150]



Fibromyalgia

Fibromyalgia is a chronic condition characterized by widespread, soft tissue pain, as well as accompanying comorbidities, such as disturbed sleep, fatigue and cognitive difficulties.[151 152] It is estimated that fibromyalgia occurs in two percent of the general U.S. population.[153] Men and children may present with the disorder; however, women are more frequently diagnosed with fibromyalgia compared to men, at a rate of nine to one.[154] Diagnosis is most likely to occur between ages 20–50.[155] Studies reporting direct medical costs demonstrate that patients with fibromyalgia cost employers approximately $6,000 a year in 1998 dollars.[156] Extrapolating from that figure, without accounting for inflation, fibromyalgia costs the U.S. health care system more than $20 billion annually.

Endometriosis

Endometriosis is a chronic neuro-endocrine-immune system disease, in which the endometrial tissue is found outside of the uterus, causing pain, infertility and other problems. The most common symptoms are pain before and during periods, pain during or after sexual activity, fatigue, infertility and heavy bleeding. Other symptoms may include painful bowel movements, painful urination, diarrhea and/or constipation and other intestinal upsets during menstruation. Endometriosis is the leading cause of chronic pelvic pain in women; however, the true prevalence of the condition is unknown because surgical confirmation is necessary to diagnose the condition.[157] It is estimated that 2 to 10 percent of women and girls in the U.S. have endometriosis; the number is most likely at least 6.3 million, or four percent.[158] Sixty percent of women develop symptoms prior to age 20.[159] Costs arising from endometriosis in women of reproductive age were estimated to be $22 billion in 2002.[160]

Chronic Headache (Migraine and Tension-Type)

Both migraine and tension-type headaches are defined as primary headache disorders, i.e., those that exist independent of another disorder. These headache disorders are classified as chronic when they occur 15 days or more a month for three months in the absence of medication use (migraine)[161] or for six months (chronic tension-type).[162] Typically, a migraine headache will affect one half of the head, is pulsating in nature, lasts from 2 to 72 hours and is generally made worse with physical activity; associated autonomic symptoms include nausea, vomiting, and sensitivity to light, sound or smell.[163] Up to one-third of those with migraine perceive an aura – a transient visual, sensory, language or motor disturbance. Chronic tension-type headache (cTTH) is characterized by pain (pressure, tightening or feeling like the head is being squeezed with a vice), frequently on both the left and right sides of the head. The pain can radiate from the lower back of the head, neck, eyes or other muscle groups. Individuals also report sensitivity to light and sound and may experience nausea. Migraine has a global prevalence of 15 percent or one billion people,[164] with 1.4 to 2.2 percent experiencing chronic migraine.[165] Chronic TTH affects 2.2 percent.[166] Both are more common in women than men.[167] Age of symptom onset for migraine ranges from 15–24 years, and cTTH most commonly begins in the teenage years.[168] [169] Nearly 10,000 lost work days a year are attributed to headache, with 42 percent of those estimated to be due to tension-type headache.[170] The U.S. direct costs of migraine are estimated at $17 billion, including $15 million in indirect costs, of which missed work is the largest component.[171]

Chronic Low Back Pain (cLBP)

Although low back pain is a symptom, according to the NIH Task Force on Research Standards for Chronic Low Back Pain (cLBP), "there is now growing evidence that in its chronic form, it can progress like other chronic pain conditions, beyond a symptomatic state to a complex condition unto itself." [172] Defined as "low back pain that occurs at least half of the days in the past six months," symptoms include dull aching, sharp pain and/or tingling or burning sensations in the low back, defined as the lumbar region of the back between the posterior margin of the rib cage and the horizontal gluteal fold. Weakness in the legs or feet may also accompany these symptoms.[173] With a worldwide lifetime prevalence of approximately 39 percent and a point prevalence of 8.1 percent in American adults, cLBP occurs from adolescence through the elderly.[174] [175] As the Task Force document summarizes, a wide range of inclusion/exclusion criteria and case definitions are used in cLBP research, making study findings difficult to interpret. This includes cost estimates for cLBP; a 2012 claims database study of nearly 40,000 cLBP patients found the direct annual cost of the disorder to be approximately $96 million, although other studies reporting simply on "low back pain" estimate the economic burden to be much higher, nearing $100 billion in direct and indirect costs annually.[176]

Table 3. Chronic Overlapping Pain Conditions – Prevalence and Symptom Onset Data

References for information contained in this table are included in the previous paragraph summaries.

Condition	Description & Symptoms	U.S. Prevalence	Symptom Onset Range
Vulvodynia	Chronic vulvar pain without an identifiable cause, including burning or other painful sensations in the vulva (external genital area) at rest and/or with touch/pressure by sitting, tampon insertion or sexual intercourse	6 million	Teens & 18–25 years
Temporomandibular Disorders	Pain and/or dysfunction in the jaw joint and muscles that control jaw movement, including dull aching pain in the face, jaw, neck, or shoulders; jaw muscle stiffness; limited movement or jaw "locking;" painful clicking, popping or grating in the jaw joint with movement; and/or change in the way teeth fit together or a bite that feels "off"	35 million	Teens to 50 years
Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome	Chronic, debilitating fatigue and other characteristic symptoms, including sleep difficulties, problems with concentration and short-term memory, flu-like symptoms, joint/muscle pain, tender lymph nodes, sore throat, headache, post-exertional relapse	Up to 4 million	10–19 & 30–39 years
Irritable Bowel Syndrome	Chronic abdominal pain or discomfort with/without changes in stool frequency or consistancy (diarrhea, constipation or mixed), which may be relieved with bowel movement	44 million	Adults under 45 years
Interstitial Cystitis/ Painful Bladder Syndrome	Chronic pelvic pain, pressure, or discomfort in the bladder/pelvis typically associated with urinary frequency and urgency, with pain during/after sex	8 million	40 years
Fibromyalgia	Widespread soft tissue pain, as well as accompanying comorbidities such as disturbed sleep, fatigue and cognitive difficulties	6 million	20–50 years
Endometriosis	Chronic pelvic pain before and/or during menstration, pain during/after sexual activity, fatigue, infertility, heavy bleeding, intestinal upset, painful bowel movements and/or low back pain with periods	6.3 million	66% before the age of 20
Headache			
Chronic Tension-Type	Pain on both sides of the head, described as pressure or tightening Sensitivity to light and sound may accompany the pain, as well as nausea	7 million	Teenage years
Chronic Migraine	Pulsating one-sided headache associated with autonomic symptoms (e.g., nausea, vomiting, sensory sensitivity), with or without aura (sensory disturbance)	7 million	15–24 years
Chronic Low Back Pain	Chronic dull aching, sharp pain and/or tingling or burning sensations in the low back, defined as the lumbar region of the back between the posterior margin of the rib cage and the horizontal gluteal fold; weakness in the legs or feet	19.5 million	Adolescence through elderly

Section IV: Research Disparities

In 2014, the National Institutes of Health (NIH), the nation's medical research agency, received $30.1 billion in taxpayer funds to fulfill its mission to improve the health of the nation.[177] The NIH supports research that extends "healthy life" and reduces the "burden of illness and disability," and studies the causes, diagnosis, prevention and cure of human diseases.[178]

Chronic pain is as prevalent as cancer, heart disease and diabetes combined, yet in 2014, as evident in Figure 4, the NIH spent 95 percent less on chronic pain research than research on these other conditions. Further, Figure 5 depicts the inordinately low ratio of NIH funding levels to societal costs for chronic pain, compared to other major diseases.

"We have some promising results, but with more research funding, and with more people having an education and understanding about pain, we could relieve suffering in millions of people."
~ Pain Physician

Figure 4. Comparison of NIH Research Spending by Prevalence of Major Diseases[179]

Combined, cancer, heart disease and diabetes affect approxiately 100 million American adults, the same number as are affected by chronic pain, yet, in FY2014, the NIH invested 95 percent less in research on chronic pain disorders.

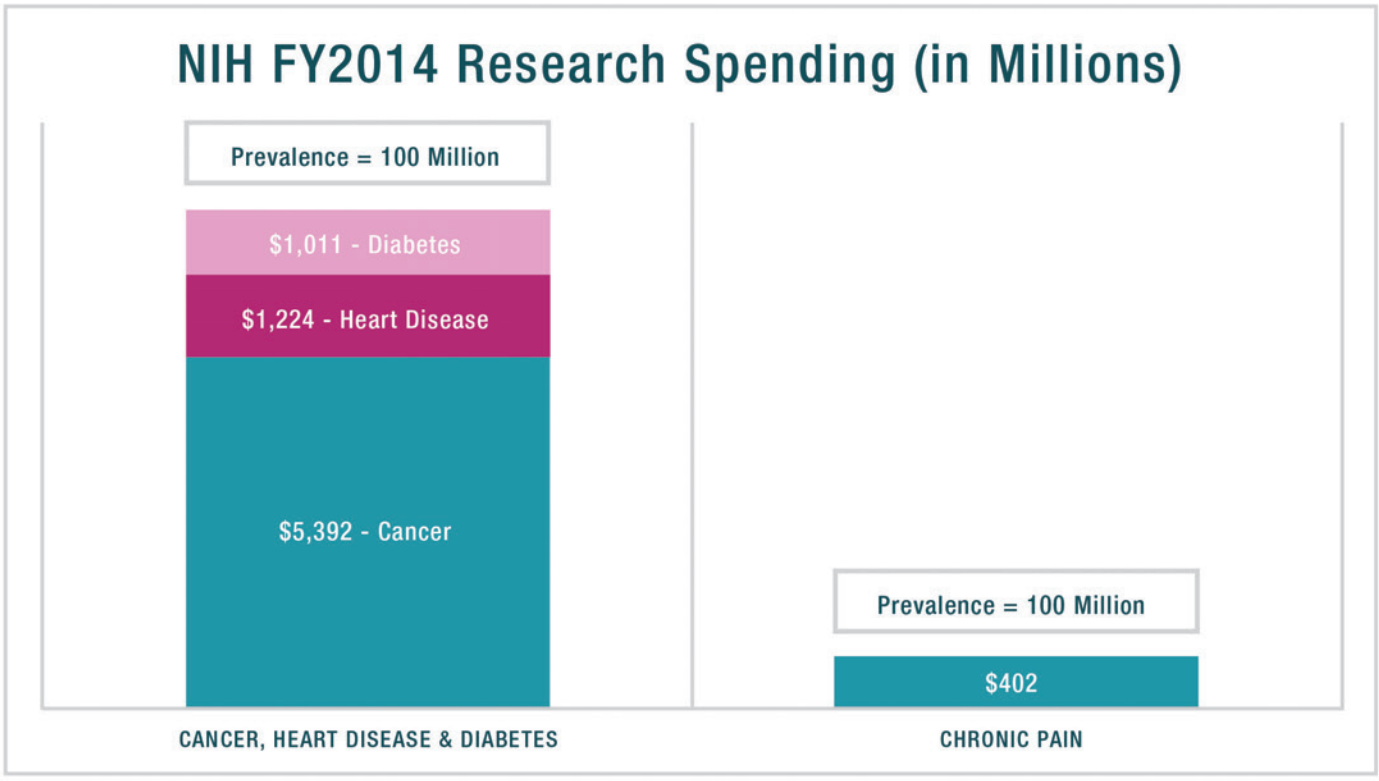


Figure 5. Comparison of FY2012 NIH Research Spending by Cost Burden of Major Diseases

This figure demonstrates the disproportionate NIH research investment in chronic pain, given its significant cost burden of $600 billion, compared to other diseases with significantly less cost burdens. Reprinted with permission. Gereau RW, et al. A pain research agenda for the 21st century. J Pain. 2014 Dec;15(12):1203-14.

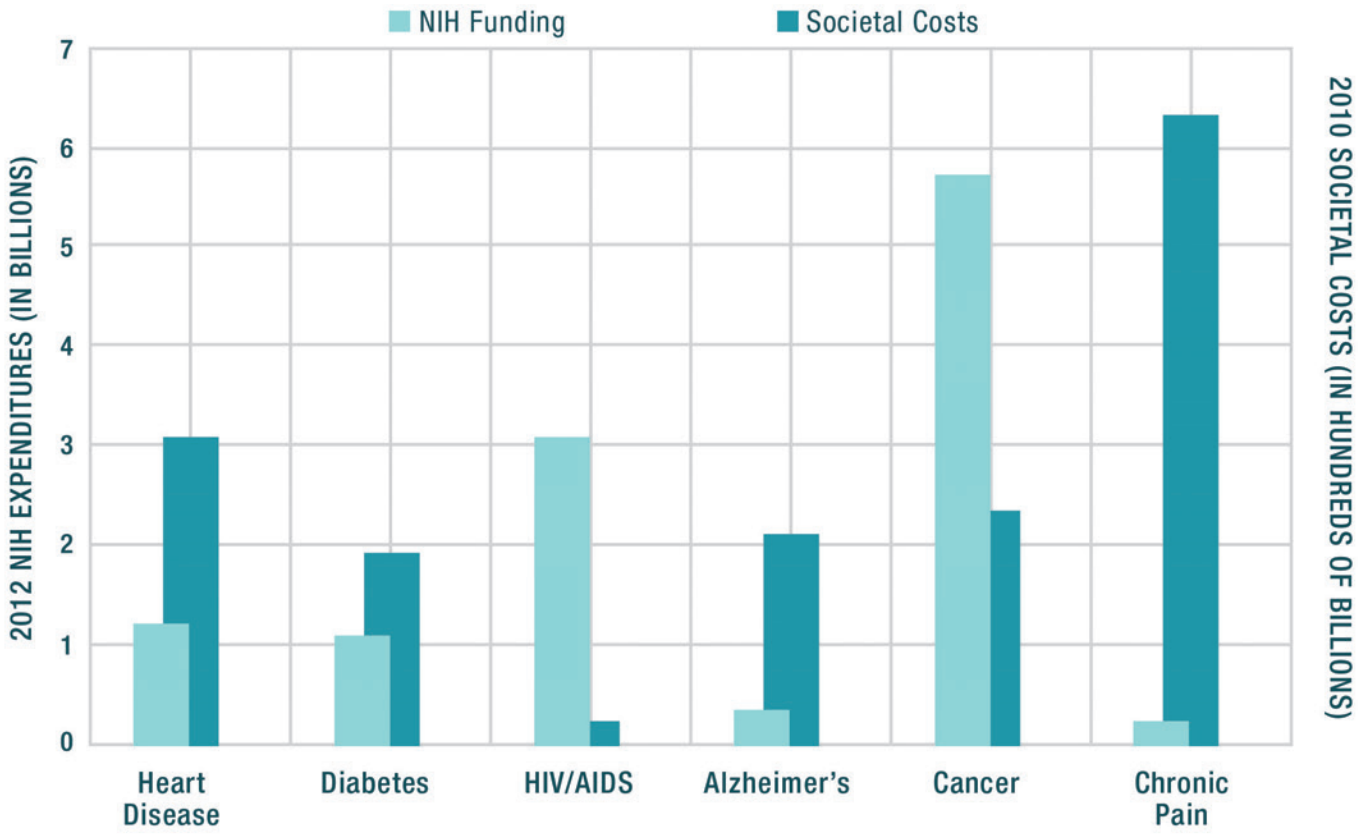
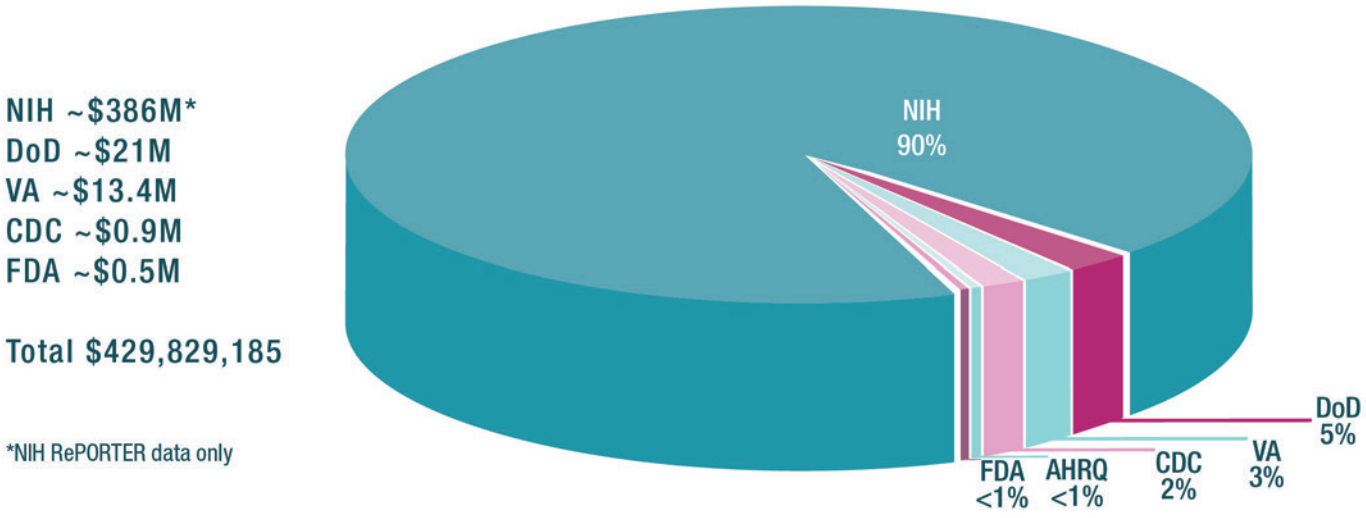


Figure 6. FY2011 Total Pain Research Expenditures by Federal Agencies

Source: Interagency Pain Research Coordinating Committee
http://iprcc.nih.gov/docs/102212_mtg_presentations/IPRCC_prelim_portfolio_analysis_508comp.pdf



Note: NIH: National Institutes of Health; DoD: Department of Defense; VA: Veterans Affairs Administration; CDC: Centers for Disease Control and Prevention; AHRQ: Agency for Healthcare Research and Quality; FDA: Food and Drug Administration

Table 4. COPCs - FY2013 & FY2014 NIH Funding Levels, Investment per Affected Individual and Primary Funding Institutes/Centers

Totals derived from NIH Research Portfolio Online Reporting Tools (RePORT) Research, Condition, and Disease Categorization (RCDC) & NIH Project RePORTER, available at http://report.nih.gov/categorical_spending.aspx & www.projectreporter.nih.gov

Condition	U.S. Prevalence	2013 NIH Funding Levels	2014 NIH Funding Levels	2013 Research Investment/Patient	2014 Research Investment/Patient	Primary NIH Funding ICs**
Vulvodynia	6 million	$4 million	$3 million	$0.67	$0.50	1 - NICHD 2 - NIDDK 3 - NINDS
Temporo-mandibular Disorders	35 million	$19 million	$18 million	$0.54	$0.51	1 - NIDCR 2 - NINDS 3 - NIEHS
Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome	4 million	$5 million	$5 million	$1.25	$1.25	1 - NIAID 2 - NINDS 3 - NINR & NIDDK
Irritable Bowel Syndrome	44 million	$23 million	$14 million	$0.52	$0.32	1 - NIDDK 2 - NCCIH 3 - NINDS
Interstitial Cystitis/ Painful Bladder Syndrome	8 million	$10 million	$9 million	$1.25	$1.13	1 - NIDDK 2 - NINDS 3 - NICHD
Fibromyalgia	6 million	$11 million	$10 million	$1.83	$1.67	1 - NIAMS 2 - NINDS 3 - NIAID, NCCIH, NINR, NIDDK
Endometriosis	6.3 million	$7 million	$7 million	$1.11	$1.11	1 - NICHD 2 - NCI 3 - NIEHS
Headache						
Chronic Tension-Type	7 million	$990,000	$285,000	$0.14	$0.04	1 - NIGMS 2 - NICHD
Chronic Migraine	7 million	$19 million	$20 million	$2.71	$2.86	1 - NINDS 2 - NIMH 3 - NICHD
Chronic Low Back Pain	19.5 million	$28 million*	$24 million*	$1.44	$1.23	1 - NCCIH 2 - NIAMS 3 - NIDA
Totals		**$127 Million**	**$110 Million**	**$1.15**	**$1.06**	

**Includes NIH investment in both "chronic low back pain" and "low back pain" studies*
***See Figure 7 for full names of NIH Institutes/Centers*

The research investment of other federal health research agenices is also incommensurate with the significant human and financial impact of chronic pain in both the general and military populations. The Interagency Pain Research Coordinating Committee conducted a trans-agency pain research portfolio analysis, the findings of which are summarized in Figure 6 for fiscal year 2011; the figures are largely unchanged in recent years.[180] This represents a meager federal research investment of $0.04 per American adult with chronic pain.

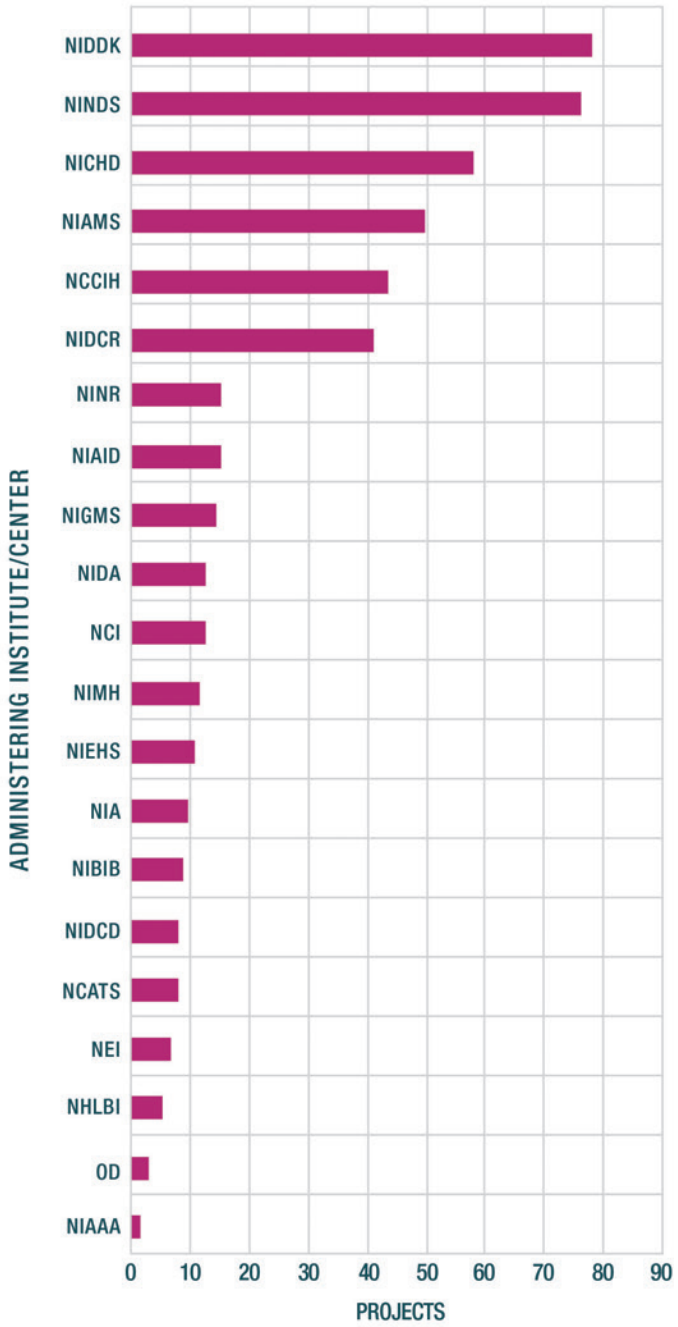
The discrepancy between the widespread prevalence and financial, economic and human toll of COPCs and NIH research funding directed toward these conditions is painfully obvious. Table 4 shows the NIH spent $110 million in 2014 on all COPCs, with an average federal investment of just $1.06 per affected individual. Further, this figure has decreased by eight percent from the 2013 investment.

"How is it possible that the country invests so little in pain research? Chronic pain has impacted every aspect of my wife's life, our marriage and family life. It has cost us so much. And we are just one of millions of families going through this. We deserve better."
~ Spouse of COPCs patient

Thirteen NIH Institutes and Centers (ICs) are primary funders of COPCs research, and 20 of the 27 NIH ICs have supported research on these conditions over the last three years (see Table 4 and Figure 7). With few exceptions, research efforts across ICs have not been coordinated or integrated.

Figure 7. NIH Institutes/Centers Funding Research on COPCs (2012–2014)

Source: NIH Research Portfolio Online Reporting Tools (RePORT)



NIH Institutes/Centers

NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases

NINDS – National Institute of Neurological Disorders and Stroke

NICHD – National Institute of Child Health and Human Development

NIAMS – National Institute of Arthritis and Musculoskeletal and Skin Diseases

NCCIH – National Center for Complementary and Integrative Health

NIDCR – National Institute of Dental and Craniofacial Research

NINR – National Institute of Nursing Research

NIAID – National Institute of Allergy and Infectious Diseases

NIGMS – National Institute of General Medical Sciences

NIDA – National Institute on Drug Abuse

NCI – National Cancer Institute

NIMH – National Institute of Mental Health

NIEHS – National Institute of Environmental Health Sciences

NIA – National Institute on Aging

NIBIB – National Institute of Biomedical Imaging and Bioengineering

NIDCD – National Institute on Deafness and Other Communication Disorders

NCATS – National Center for Advancing Translational Sciences

NEI – National Eye Institute

NHLBI – National Heart, Lung, and Blood Institute

OD – Office of the Director

NIAAA – National Institute on Alcohol Abuse & Alcoholism

Section V: FDA-Approved Therapies - Safety and Efficacy

Given their widespread prevalence and financial toll, significant rates of overlap, similar symptom presentation, common disease mechanisms and appreciable unmet treatment demand, there is a tremendous opportunity for research and development of safe and effective treatments for chronic overlapping pain conditions (COPCs). As a result of the meager federal, private and industry research investment in COPCs to date, evidence-based treatment options are woefully few and inadequate. Furthermore, as Table 5 summarizes, only a handful of FDA-approved pharmaceutical treatments exist for half of these conditions, only two of which have been approved in the last five years. None are indicated for more than one COPC, although several are used off-label to treat a number of these conditions. The resultant situation is that COPCs sufferers and their clinicians must use trial-and-error methods selected from a myriad of treatments, most with unknown safety and efficacy data (especially when combined), until they identify a combination that brings some relief. Table 6 summarizes the findings of recent systematic reviews describing the poor state of evidence on the efficacy of treatments for COPCs.

"As my health has continued to decline with the development of additional COPCs, I've spent countless hours experimenting with dozens of treatments that have easily cost us tens of thousands of dollars. Only a few have been somewhat helpful. Most have not only been ineffective, but have caused other health issues and serious side effects. My doctors and I are equally frustrated that the scientific evidence we need to make informed choices about my health care is just not available."

~ COPCs patient

Table 5. FDA-Approved Pharmaceutical Treatments for COPCs

Condition	FDA - Approved Therapies	Company	Date Approved
Vulvodynia	None		
TMD	None		
cTTH	None		
ME/CFS	None		
cLBP	None		
Chronic Migraine	Botox®	Allergan	2010
Migraine (Other)	Amerge®	GlaxoSmithKline	1998
	Axert®	Pharmacia & Upjohn	2001
	Bayer Extra Strength®	Bayer	2001
	Cambia®	Kowa Pharmaceuticals	2009
	Depakote®	Abbott Laboratories	1996
	Depakote ER®	Abbott Laboratories	2000
	Excedrin Migraine®	Bristol Meyers Squibb	1998
	Frova®	Elan Pharmaceuticals	2001
	Imitrex®	GlaxoSmithKline	1997
	Maxalt®	Merck	1998
	Migranal®	Novartis	1997
	Relpax®	Pfizer	2002
	Stavzor®	Banner Pharmacaps	2008
	Zomig®	AstraZeneca	2001
IBS	Linzess®	Forest Labs & Ironwood Pharmaceuticals	2012
	Lotronex®	GlaxoSmithKline	2000
	Zelnorm®	Novartis	2002
IC/PBS	Elmiron®	IVAX	1996
Fibromyalgia	Savella®	Forest Labs	2009
	Lyrica®	Pfizer	2007
	Cymbalta®	Eli Lilly	2008
Endometriosis	Lupron Depot®	TAP Pharmaceuticals	1999

Table 6. Findings of Systematic Reviews and Evidence Grading Demonstrate Poor Evidence of Treatment Effectiveness Across all 10 COPCs and the Urgent Need for Well-Designed and Conducted Efficacy Studies

Condition	Publication Source	Publication Aim	Conclusion
Vulvodynia	Systematic Review & Evidence Grading	Assess the benefits and harms of interventions for vulvodynia. Each modality was assessed with a system similar to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system.[181]	"Although there are many interventional therapies, and their use is increasing, there is also uncertainty or controversy about their efficacy. There was fair evidence of lack of efficacy for several non-surgical interventions. There were several interventions for which there were insufficient evidence to reliably evaluate. There was insufficient evidence to judge harms or long-term benefits. Providers and patients looking for evidence-based interventions for vulvodynia may need to rely on indirect evidence from studies of neuropathic pain and functional pain syndromes."[182]
Temporo-mandibular Disorders	Systematic Review	Assess the effectiveness of pharmacological interventions in relieving pain in chronic TMD.	"TMDs are treated with a wide range of drugs. The extent to which the use of these drugs is based upon evidence is unknown. No meta-analysis was conducted due to lack of similarities across the included studies. There is insufficient evidence to support or not support the effectiveness of the reported drugs for the management of pain due to TMD. There is a need for high quality randomized clinical trials to derive evidence of the effectiveness of pharmacological interventions to treat pain associated with TMD."[183]
	Cochrane Reviews	Assess the effectiveness of non-pharmacological treatments for TMD.	Several reviews found insufficient consistent evidence to either support or refute the use of many non-pharmacological treatments for TMD, and further highlighted the need for well-designed and conducted trials to assess efficacy.[184-186]
Myalgic Encephalo-myelitis/ Chronic Fatigue Syndrome	Systematic Review	Substantive update of a systematic review published in 2002.[187] Seventy studies on pharmacological and non-pharmacological treatments were reviewed.	"Graded exercise therapy and cognitive behavior therapy appeared to reduce symptoms and improve function based on evidence from randomized controlled trials. For most other interventions, evidence of effectiveness was inconclusive and some interventions were associated with significant adverse effects."[188]
Irritable Bowel Syndrome	Systematic Review & GRADE Evaluation	Answer the question: What are the effects of treatments in people with IBS?	Of 12 mainstay treatments for IBS, the majority (9), were graded with 'low' or 'very low' evidence of symptom improvement and quality of life.[189] Evidence is limited and more well-designed studies are required to better inform therapeutic decision-making in the management of this difficult syndrome.[190]
Interstitial Cystitis / Painful Bladder Syndrome	Systematic Review	The review yielded an evidence base of 86 treatment articles. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low).	The majority of therapies yielded Level C evidence, with only a couple meeting an evidence Level B, and one Level A.[191]

Table 6. Findings of Systematic Reviews and Evidence Grading Demonstrate Poor Evidence of Treatment Effectiveness Across all 10 COPCs and the Urgent Need for Well-Designed and Conducted Efficacy Studies *(cont.)*

Condition	Publication Source	Publication Aim	Conclusion
Fibromyalgia	Review, Evidence Grading & Clinical Guideline	Assess the current evidence on the efficacy of treatments for FM in developing clinical guidelines.	"Although there is copious literature available addressing various aspects of FM, the level of evidence available, other than for more recent drug studies, is mostly poor or lacking completely, with more than two-thirds of the recommendations graded as either level D or consensus." [192]
	AHRQ Comparative Effectiveness Review	Compare the effectiveness of treatments in subgroups of highly affected or clinically complex adults with FM.	"Overall treatment effects were small and even less when substantial placebo-group improvements were considered." [193]
Endometriosis	Overview of Cochrane Reviews	Summarize evidence from 17 Cochrane systematic reviews on treatment options for women with pain or subfertility associated with endometriosis. Fourteen reviews on pain relief assessed drug and non-drug treatments.	"The quality of the evidence for specific comparisons ranged from very low to moderate. Limitations in the evidence included risk of bias in the primary studies, inconsistency between the studies, and imprecision in effect estimates. Evidence on harms was scant, but GnRH analogues, danazol and depot progestagens were associated with higher rates than other interventions." [194]
Chronic Tension-Type Headache	Systematic Review & GRADE Evaluation	Answer the question: What are the effects of drug and non-drug treatments for cTTH?	All but one treatment had 'very low' or 'low' evidence, which was acupuncture with 'moderate' evidence. [195]
Chronic Migraine	AHRQ Comparative Effectiveness Review	Assess the comparative effectiveness and safety of preventive pharmacologic treatments for community-dwelling adults with episodic or chronic migraine.	"For chronic migraine, onabotulinumtoxin A reduced migraine attacks but increased the risk of adverse effects and treatment discontinuation due to adverse effects. We could not determine the long-term (i.e., trials of more than 3 months duration), preventive benefits and adherence with drugs. Evidence on improving quality of life was inconsistent across individual drugs. Evidence for individualized treatment decisions is very limited. Future research should examine the role of patient characteristics on drug benefits and safety." [196]
Chronic Low Back Pain	Report of the NIH cLBP Task Force Evidence-Based Review	N/A	"Many classes of interventions have been developed and tested in adults with cLBP… Many of these have shown some clinical benefit, but few appear to consistently provide substantial, long-term reductions in pain with increased function." [197]

Section VI: Emerging Research on Common Underlying Disease Mechanisms

In addition to a growing epidemiological evidence base substantiating the overlap of conditions addressed in this report, several observations support the concept that these conditions share common underlying mechanisms of disease. Those affected by chronic overlapping pain conditions (COPCs) are more likely to be female, exhibit similar symptom profiles and benefit from similar treatments. Studies increasingly support the idea that COPCs are heterogeneous and that patient populations – both within and across disorders – cluster into phenotypic subgroups with common pathophysiologic mechanisms, and each being responsive to treatment modalities that specifically target those mechanisms.[198] This section summarizes the findings of emerging research on common underlying mechanisms of disease in COPCs.

Genetic and Environmental Factors

Pain genetics research demonstrates that there are likely numerous genetic variations that determine the sensitivity of an individual's nervous system to pain and other sensory input, as well as risk for developing chronic pain.[199-201] Studies have identified a number of genetic variations associated with a higher risk of developing COPCs, most of which involve the regulation of the immune, neural and endocrine systems, specifically related to sensory/pain processing.[202-217] Likewise, research demonstrates a strong familial component to developing COPCs.[218-224] Twin studies have been particularly helpful in establishing that COPCs co-aggregate, are strongly genetic and are separable from anxiety and depression.[225-232] Gene expression studies in this area are also beginning to yield insight on molecular pathways implicated in symptom expression and treatment response.[233-236] As with most illnesses that have a genetic underpinning, environmental factors, such as infection, trauma, surgery and injury, may play a prominent role in triggering the onset of COPCs.[237-248] Genome-wide epigenetic studies have not yet been conducted to assess the molecular basis of various environmental factors in the etiology of these disorders. Once COPCs are triggered, the factors and mechanisms responsible for ongoing symptom expression are complex and multifactorial.

Abnormal Pain and Sensory Processing

Once COPCs develop, the abnormalities most consistently detected are pain and sensory processing dysfunction. Compared to healthy individuals, those with COPCs report enhanced pain perception – both increased pain intensity and lower sensory and pain thresholds – with the application of a variety of sensory stimuli (e.g., pressure, thermal, vibratory, electrical). These sensitivities are found not only at the body site where a person experiences chronic pain, but at distal locations, such as the thumb, shin and arm.[249-275] Recent studies, including those utilizing functional MRI, also provide evidence that other sensory input, such as light, sound and odor, are biologically amplified in patients with COPCs.[276-281] In these studies, the insula – the brain region that plays a critical role in sensory integration – most consistently shows hyperactivity.[282 283]

Using experimental pain testing, two pathogenic mechanisms have been found to contribute to enhanced pain perception and low sensory thresholds in individuals with COPCs:

- **Attenuated Diffuse Noxious Inhibitory Control (DNIC)/ Conditioned Pain Modulation (CPM)**

  In healthy people as well as lab animals, application of an intense painful stimulus for two to five minutes produces generalized whole-body analgesia, i.e., "pain inhibits pain." This analgesic effect has been consistently observed to be attenuated or absent in many, but not all, individuals with COPCs.[284-297]

- **Increased Wind-Up/Temporal Summation**

  Studies also suggest that some individuals with COPCs exhibit evidence of "wind-up" or temporal summation, in which repeated painful stimuli cause increased pain perception, indicative of sensitization of the central nervous system.[298-308]

Autonomic Nervous System Abnormalities

Increased sympathetic-to-parasympathetic balance has been demonstrated in some subgroups of individuals with COPCs, raising the possibility that dysfunction of the autonomic nervous system could be among one of the common clustering pathophysiologic mechanisms.[309-316]

Neuroimaging Abnormalities

A growing body of evidence shows that individuals with COPCs are more likely to exhibit changes in gray and white matter volume and cortical thickness in various brain regions. These findings closely align with what is increasingly reported in the general pain research literature – that chronic pain may be a neurodegenerative disorder.[317-329] These subtle changes in size and shape of cortical and sub-cortical areas in chronic pain states are improving our knowledge of "neuroplasticity," a term that is probably much more accurate than "neurodegeneration," since studies have found reversal of imaging findings following treatment.[330 331]

Functional neural imaging (i.e.,fMRI) provides a visual picture of how the brain processes the sensory experience of pain. Studies of people with COPCs indicate that in response to painful stimuli, similar brain regions, including those that integrate and process sensory information, cognition and affect, show increased activity or are "activated."[332-347] A more recent advance in the use of fMRI is to look at patterns of connectivity among different brain regions, either while a person is at rest or performing a specific task.[348] A resting state analysis enables one to evaluate brain changes associated with chronic spontaneous pain, as well as examine how chronic pain may disrupt non pain-related functions, such as cognition. Functional connectivity studies of individuals with COPCs show altered connectivity among several regions of the brain, such as the default mode, executive attention, pain modulatory and sensory-motor networks.[349-359] This technique holds considerable promise in identifying potential biomarkers for pain intensity and underlying mechanisms.

CNS v. PNS Contribution

Several hypotheses have been proposed regarding the relative contribution of the peripheral nervous system (PNS) and the central nervous system (CNS) in the development and maintenance of COPCs. One theory is that they both exert influence on a continuum. In individuals with mild to moderate symptoms, there may be a greater contribution from the PNS (e.g., upregulation of afferent pathways), which is influenced by environmental factors, such as infection or injury. In those with moderate to severe symptoms, the CNS is proposed to have a greater contribution, resulting in disinhibition of CNS pain processing, which then leads to a lack of pain inhibition in the PNS. Further, with increasing severity and number of pain symptoms (i.e., COPCs), contributory factors, such as life stressors, poor coping and mood alterations, become more prevalent.[360] What is unclear at this time is whether the CNS dysfunction can be the sole source of pathogenesis, as some studies demonstrate that persistent nociceptive input from the PNS is needed to maintain CNS abnormalities.[361-365]

Female Predominance and Role of Ovarian Hormones

COPCs have a female predominance, proposed to result from multiple factors.[366] Basic science studies suggest that ovarian hormones have distinct effects on inflammation, affective states, stress response, modulatory pain systems and afferent sensory systems that increase or decrease pain reactivity.[367 368] Clinical studies demonstrate alterations in pain severity, thresholds and tolerance during different phases of the menstrual cycle,[369-372] and recent neural imaging studies have even indicated important sex differences in the connectivity between brain regions that process emotion and cognition.[373] Advancing knowledge of the mechanisms by which ovarian hormones modulate pain is necessary and will aid in understanding why pain tends to be more frequent, severe and disabling in women.[374 375]

Neuroendocrine and Neuroimmune Abnormalities

Chronic pain research establishes that there is a complex interplay among immune cells, glia and neurons – through the release of inflammatory mediators and interactions with neurotransmitters and their receptors – that affects immune response and modulates pain pathways and sensitivity in both the peripheral and central nervous systems.[376-378] Studies of COPCs indicate that a host of immuno-inflammatory mediators, both in the bloodstream and in painful peripheral tissues, are altered and play a role in the development and/or maintenance of these conditions in at least a subgroup of patients.[379-390]

The hypothalamic-pituitary-adrenal (HPA) axis consists of complex interactions among these three endocrine glands that control stress and regulate a wide array of body functions, such as immunity, digestion, emotion and energy storage. Overall, although study results are inconsistent, HPA axis dysregulation appears to play a role in at least a subset of those with COPCs.[391-403] This may not be surprising given that baseline and stimulated HPA axis functions are highly dynamic and affected by many factors. One hypothesis is that

early dysregulation of the HPA axis results in elevated HPA axis hormone levels, whereas more prolonged dysfunction ultimately leads to blunted cortisol levels due to ineffective HPA axis responsiveness.[404]

Role of Stress, Behavioral and Psychological Factors

The role of adverse childhood experiences, early life (and/or ongoing) stress, and behavioral and psychological factors are known to play a role in the incidence and maintenance of many chronic illnesses, including type 2 diabetes, heart disease and cancer.[405-408] Studies demonstrate that the relationship between chronic pain and distress is complex, and that distress can both be an incident factor and a consequence of chronic pain.[409 410] In this latter situation, individuals experience difficulty functioning in their various roles after developing COPCs, which can exacerbate symptoms and lead to maladaptive illness behaviors. Using statistical clustering models and other types of research, studies are beginning to identify distinct subgroups of patients with COPCs with similar profiles related to symptom severity, pain/sensory sensitivity and psychosocial functioning, identifying those who are either more susceptible or resilient to chronic pain and its biopsychosocial effects.[411-413]

Table 7. Mechanistic Characterization of Chronic Pain

A mechanistic approach to pain requires that clinicians assess whether an individual has nociceptive (peripheral inflammation or damage), neuropathic pain (due to nerve damage) and/or central pain (due to abnormal sensory processing in the brain and/or spinal cord, i.e., central nervous system) and base treatment on this characterization rather than diagnostic label, e.g., headache, fibromyalgia.

	Peripheral (Nociceptive)	Neuropathic	Centralized
Pathogenesis	Primarily due to inflammation or mechanical damage in peripheral tissue	Damage or entrapment of peripheral nerves	Primarily due to abnormal pain processing in the central nervous system although maintenance may require persistent PNS input
Favorable Treatment	NSAIDs, opioids, procedures (including surgery)	Pharmacological therapy targeting peripheral and central nervous systems	Neuroactive compounds affecting the central nervous system (SNRIs, tricyclic antidepressants, anticonvulsants)
Behavioral Factors	Minor	N/A	Prominent
Examples	Osteoarthritis Rheumatoid arthritis Cancer pain	Diabetic neuropathy Post-herpetic neuralgia	Chronic Overlapping Pain Conditions

Section VII: Promising National Studies and Validated Instruments for Clinical Research

Promising National Research Studies

Research on chronic overlapping pain conditions (COPCs) has been the frontrunner in multi-disciplinary phenotype-based research. Studying risks, causes, mechanisms and treatment across conditions, rather than in duplication in each individual condition is not only a cost-effective approach, but one that will parse out both what is common and unique among COPCs subgroups. Further, employing a systems-based research approach to COPCs is both holistic and patient-centric. Presently, there are three national multi-center studies in various stages of development, execution and publication. This section provides a brief summary of each with references for additional information.

These multi-site national research collaborations have begun to advance a comprehensive scientific approach to understanding the epidemiology and pathophysiology of COPCs. A coordinated expanded basic, translational and clinical research effort that addresses all COPCs is needed. In addition, collaborative initiatives – throughout the research and development process – that include academia, industry, government agencies, service and reimbursement sectors, clinical care, nonprofits and philanthropy are required to translate scientific discoveries into meaningful clinical change for individuals suffering from COPCs. The next and final section of this report summarizes the recommendations CPRA has put forth to do so.

Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network

The MAPP Network is a National Institutes of Health (NIH)-sponsored, multi-center study of urologic chronic pelvic pain syndrome (UCPPS) – a term used to encompass both interstitial cystitis/painful bladder syndrome and chronic prostatitis/chronic pelvic pain syndrome – designed to provide new insights into underlying etiology, natural history and risk factors associated with the development of UCPPS. In 2008, the MAPP Network was initiated by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) under a cooperative agreement for a five-year funding period. It is comprised of six Discovery Sites, a Data Coordinating Center, a Tissue and Technology Core and other units. With the goal of establishing a translational foundation for improved clinical management, the MAPP Network's objective is to advance understanding of disease phenotypes; underlying pathophysiology; treated natural history; and biologic, genetic, and behavioral risk factors for UCPPS. An important aim of this program is to better understand the biologic and behavioral relationships between UCPPS and co-morbid non-urologic pain syndromes. Those of primary interest are fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, vulvodynia and migraine headache. To date, the Network has recruited over 1,000 study participants who have undergone extensive phenotypic characterization through complementary, integrated network protocols. Importantly, all clinical data is centrally managed and analyzed by the Data Coordinating Center allowing integration of multiple scientific domains. Presently, the MAPP Network is developing numerous manuscripts describing symptoms, patient subsets, biomarkers and structural/functional neuroimaging results. A number of these studies have already been published,[414-420] including two that provide a comprehensive overview of the project and its methodology.[421 422]

The NIDDK, with supplemental funding from the NIH Office of Research on Women's Health, recently renewed support for a second five-year project period, MAPP II, which began in 2014. NIH funds will support the current Discovery Sites and Cores and the addition of three new Discovery Sites through the NIDDK RFA, "Expansion of the MAPP Research Network," described here: http://grants1.nih.gov/grants/guide/rfa-files/RFA-DK-13-025.html. These sites are currently developing a set of collaborative protocols for the second project period. Studies are expected to broadly focus on predictors of symptom progression and resolution, and understanding different mechanism-based phenotypic subgroups that respond differently to treatment.

Additional information can be viewed online at:
www.mappnetwork.org

Orofacial Pain, Prospective Evaluation and Risk Assessment (OPPERA)

In 2006, the National Institute of Dental and Craniofacial Research (NIDCR) funded this first-of-its-kind comprehensive program project, led by William Maixner, PhD, DDS, director of the University of North Carolina Center for Neurosensory Disorders – a multidisciplinary research team of accomplished pain clinicians and researchers, psychophysiologists, molecular and cellular geneticists, biostatisticians and epidemiologists. The OPPERA study – a seven-year, four-site, cross-disciplinary, prospective investigation of temporomandibular disorders (TMD) – sought to identify putative physiological and psychological risk factors, clinical characteristics and related genetic mechanisms that influence the development of chronic orofacial pain associated with TMD. Additionally, it aimed to characterize the biological pathways through which genetic variations causally influence TMD risk. Investigators enrolled and monitored 2,700 men and women aged 18 to 44 years, 260 of whom developed TMD in the three-year follow-up period. Since OPPERA's first publication in 2011, 20 papers summarizing the study's expansive findings collectively demonstrate that TMD is a complex disorder with multiple causes consistent with a biopsychosocial model of illness, and that it is no longer appropriate to regard TMD solely as a localized orofacial pain condition.[423-442]

"I've been suffering for years. I had to retire and am on disability due to these conditions. Please continue to explore the relationship among these diseases to offer some hope to those of us who are so ill."
~ Marilyn, COPCs patient

Of the 260 people followed in OPPERA I who developed TMD in the three-year follow-up period, risk factors for acute TMD significantly differed from genetic and phenotypic risk factors for chronic TMD. Further, 86 percent of chronic TMD cases had one or more of four chronic overlapping pain conditions (COPCs): headache, low back pain, irritable bowel syndrome or widespread body pain. Building upon these findings, OPPERA II – the second five-year phase of the study funded by NIDCR in 2012 – aims to identify phenotypes and genotypes that predict risk of transition from acute to chronic TMD, risk factors for one or more of the previously mentioned COPCs and genetic variants associated with chronic TMD. In doing so, they are following a group of 1,000 adults with acute TMD for six months and conducting follow-up assessments from those participating in the OPPERA I study to identify those with one or more COPCs. Existing phenotypes and genotypes measured at baseline are being used to predict risk of developing one versus two-or-more COPCs relative to controls. A discovery-phase genome wide association study (GWAS) will use existing DNA from 1,000 OPPERA I chronic TMD cases and the same number of OPPERA I controls, and replicate findings in another cohort of 2,000 cases and controls. Findings will be contrasted with GWAS analysis of the acute-TMD cohort to identify the genes that contribute differentially to acute and chronic TMD. Based on these findings and validated associations from other studies, twelve genes will be selected for exon sequencing of rare genetic variants. Knowledge generated from these proposed studies will significantly impact scientific understanding of risk factors for COPCs. Moreover, the findings will be of direct benefit to clinicians and their patients, elucidating mechanisms underlying chronic idiopathic pain in people with TMD.

For additional information on OPPERA I & II, visit:
www.nidcr.nih.gov/Research/ResearchResults/InterviewsOHR/TIS012006.htm
http://projectreporter.nih.gov/project_info_description.cfm?aid=8525386&icde=19436520

Complex Persistent Pain Conditions: Unique & Shared Pathway of Vulnerability

This program project, also led by Dr. Maixner and the UNC Center for Neurosensory Disorders and funded in 2011 by the National Institute of Neurological Disorders and Stroke, expands upon OPPERA I & II to specifically study four prevalent pain conditions that frequently co-occur with TMD: vulvodynia, irritable bowel syndrome, episodic migraine and fibromyalgia. Fundamental to the aims and goals of this study are that the etiology of these COPCs is multifactorial and their clinical manifestations diverse. Further, a unifying hypothesis integrating this study is that multiple genetic factors, when coupled with environmental exposures (e.g., injury, infections, physical and psychological stress), increase susceptibility to COPCs by enhancing pain sensitivity and/or increasing psychological distress. This project seeks to identify risk factors, clusters, and associated genetic polymorphisms that influence pain amplification and psychological distress in study participants who have established COPCs. Additionally,

investigators aim to characterize the biological pathways through which these genetic variations causally influence the development of COPCs. Their analyses will characterize clusters of patients within each condition that vary significantly according to disease manifestation and non-pain domains (e.g., fatigue, sleep). Importantly, the team expects some clusters of patients to be more alike across COPCs than within any single COPC diagnosis.

Additional information can be viewed online at:
http://grantome.com/grant/NIH/P01-NS045685-09

Validated Research Instruments Used in Clinical COPCs Research

Decades of pain research has led to the understanding that it is insufficient to simply measure pain severity in studies of individuals with chronic pain and COPCs. Multiple domains (e.g., mood, sleep, fatigue, cognition, functional status) are of relevance and interact to determine disease severity, outcomes and progression. For example, IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) has identified relevant domains beyond pain severity that should be included in any pain-related clinical trial and include the following: pain intensity, physical functioning, emotional functioning, patient global impression of change, comorbid symptoms and adverse events.[443] Likewise, OMERACT (Outcome Measures in Rheumatology) has studied and identified domains (in addition to pain severity) that are endorsed by both patients and treating clinicians as being important to assess when considering fibromyalgia. These include tenderness, fatigue, patient global impression of change, physical and emotional functioning, sleep disturbance, depression, dyscognition, stiffness and anxiety.[444] Investigators studying specific COPCs will often find it necessary to utilize condition-specific measures, such as measures of fatigue in ME/CFS patients, bowel habits in IBS patients, voiding patterns in IC and pelvic floor muscle dysfunction in vulvodynia patients. However, a core set of domain measures that cut across COPCs (e.g., mood, sleep, physical function) are useful for characterization, subtyping of COPCs patients and providing insight into common underlying mechanisms. Core domains and examples of assessment instruments are contained in Table 8 (adapted from Williams, Opinions in Urology, 2013).[445]

Many investigators have also begun to utilize the NIH-sponsored initiative, PROMIS (Patient Reported Outcomes Information System), which includes computer-adaptive-testing to ease patient reporting burden and provides measure comparison to national means. PROMIS has developed a core set of questions that could address common domains of relevance for a broad range of chronic illnesses (e.g., pain, physical functioning, fatigue, emotional status, sleep problems, cognition). These measures are designed to be applied across conditions and are scaled using a common metric so that comparisons across conditions can be made. Many, but not all, of the PROMIS measures have been (or are in the process of being) validated against older standardized measures such as those listed in Table 8. For additional information on the many fixed-item and computer adapted assessment tools, see the PROMIS Assessment Center at www.assessmentcenter.net.[446]

Table 8. Examples of Assessment Instruments by Domain for Chronic Pain

Domain	Purpose	Instrument
Pain Symptom	Pain Intensity	VAS,[447] NRS, VRS
	Pain Quality	MPQ[448]
	Pain Distribution	WPI[449]
	Combination: Intensity/Distribution/Quality	PainDetect[450]
Co-Morbid Symptoms (including physical function)	Fatigue	MFI[451]
	Sleep Problems	PSQI[452]
	Perceived Cognitive Problems	MASQ[453]
	Functional Status	SF36,[454] WHODAS 2.0[455]
	Combination: Intensity/Functional Interference	BPI[456]
	Combination: Functional Symptom Checklist	PILL[457]
	Combination: Functional Symptom Checklist	CMSI[458]
	Combination: Functional Symptom Checklist	SSI[459]
Affective Vulnerability	Depressed Mood	CESD[460]
	Anxious Mood	STAI[461]
	Anger	STAXI[462]
	Combination: Depression/Anxiety	HADS[463]
	Combination: Negative/Positive Affect	PANAS[464]
Beliefs and Attitudes	Locus of Pain Control	BPCQ[465]
	Coping Strategies	CSQ[466]
	Self-Efficacy to Manage Pain	SEQ[467]
	Catastrophizing	PCS[468]
Environmental/Social	Couple Marital Satisfaction	DAS[469]
	Combination: Work, Family, Social	WHYMPI[470]
	Social Participation (Enfranchisement)	PE[471]

Note: Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), Verbal Rating Scale (VRS); McGill Pain Questionnaire (MPQ); Widespread Pain Index (WPI); Multidimensional Fatigue Inventory (MFI); Pittsburgh Sleep Quality Index (PSQI); Multiple Abilities Symptom Questionnaire (MASQ); Short Form 36 (SF36); World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0); Brief Pain Inventory (BPI); Pennebaker Inventory of Limbic Languidness (PILL); Complex Medical Symptom Inventory (CMSI); Symptom Severity Index (SSI); Center for Epidemiologic Studies Depression Scale (CESD); State Trait Anxiety Inventory (STAI); State Trait Anger Expression Inventory (STAXI); Hospital Anxiety and Depression Scale (HADS); Positive and Negative Affect Scale (PANAS); Beliefs in Pain Control Questionnaire (BPCQ); Coping Strategies Questionnaire (CSQ); Self-Efficacy Questionnaire (SEQ); Pain Catastrophizing Scale (PCS); Dyadic Adjustment Scale (DAS); West Haven Yale Multidimensional Pain Inventory (WHYMPI); Participation Enfranchisement (PE)

Section VIII: Recommendations for Advancing Research

Learning from Past Successes and Failures

The NIH Pain Consortium recently established the NIH Task Force on Research Standards for Chronic Low Back Pain (cLBP) after a review of cLBP studies demonstrated that researchers use "variable inclusion and exclusion criteria, case definitions for LBP chronicity or recurrence, baseline assessments, stratification criteria, and outcome measures," and that "as a result, it is difficult to compare studies of similar or competing interventions, replicate findings, pool data from multiple studies, resolve conflicting conclusions, develop multidisciplinary consensus, or even achieve consensus within a discipline regarding interpretation of findings." [472] The resultant manuscript summarizes the Task Force's recommendations for definitions, a minimum dataset, reporting outcomes, and future research.[473] The NIH Pain Consortium has approved the recommendations, which investigators are now asked to incorporate into their NIH grant applications. The Task Force believes that these recommendations will advance the field, help to resolve controversies, and facilitate future research, as greater consistency in reporting should facilitate comparison among studies.

Deliberations of the August 2012 Workshop on Chronic Overlapping Pain Conditions (COPCs) revealed almost identical findings. As no Research Diagnostic Criteria (RDC) for COPCs currently exist, investigators from different institutions are using different ontology, case definitions and outcome measures. High-caliber research on COPCs has recently begun and we have a historic opportunity – responsibility even – to ensure that current and future research efforts are conducted in a strategic coordinated fashion. This will maximize the federal investment in COPCs research and reduce taxpayer waste from incomparable study findings. Most importantly, this will benefit those for whom scientific research is conducted – individuals affected by these life-altering disorders.

We have an obligation to learn from both the prior successes and shortcomings of cLBP research and other disorders, and an ethical responsibility to incorporate lessons learned into future research efforts for all diseases, including COPCs. The most urgently needed initiatives for various federal, private and corporate entities are summarized as follows.

Vision for the Future

With an increased federal and private investment to implement the initiatives called for by the Chronic Pain Research Alliance, taxpayer dollars would be maximized through a coordinated, standardized and collaborative research effort, generating urgently needed scientific evidence on chronic overlapping pain conditions. This evidence would be used to develop diagnostic and treatment guidelines for the training of health care professionals, enabling them to provide high-quality, evidence-based medical care to those suffering from these life-altering conditions, improving their health, quality of life, dignity and ability to fully contribute to society.

Basic, Translational and Clinical Research

National Institutes of Health (NIH) | Patient Centered Outcomes Research Institute (PCORI) | Department of Veterans Affairs (VA) | Department of Defense (DoD) | Industry

A comprehensive, coordinated and cost-effective effort – that spans the basic, translational and clinical research continuum – is urgently needed to advance understanding of the risks, causes and mechanisms of COPCs, and should yield safe and effective treatments for these disorders. The NIH should lead this effort through the developed Trans-NIH Working Group on Chronic Overlapping Pain Conditions, and should include all relevant agencies and organizations, such as the Patient Centered Outcomes Research Institute, Department of Defense and Department of Veteran Affairs. The research recommendations put forth from the August 2012 Workshop on Chronic Overlapping Pain Conditions should be used as a starting point. Further, in an effort to maximize the research investment in COPCs research, the large program projects already funded by the NIH and described in the prior section (MAPP, OPPERA, etc.), should be expanded upon to include all COPCs.

Research Diagnostic Criteria, Common Data Elements & Data Repository

National Institutes of Health (NIH)

The purpose of the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDE) Project, "is to standardize the collection of investigational data in order to facilitate comparison of results across studies and more effectively aggregate information into significant metadata results," and central to this project "is the creation of common definitions and data sets so that information (data) is consistently captured and recorded across studies."[474]

As previously mentioned, investigators currently studying COPCs are using various definitions and diagnostic criteria, as well as collecting a wide range of data using different methods, leading to great difficulty in comparing study findings across publications, research groups and institutions. The NIH should swiftly lead an effort that includes other federal agencies (e.g., Centers for Disease Control and Prevention, Department of Veterans Affairs, Department of Defense) to develop Research Diagnostic Criteria (RDC), a case definition and data dictionary for COPCs and require applicants to use these criteria in their grant proposals. Further, to maximize the federal investment in COPCs research and reduce waste from incomparable study findings – now, as high-quality COPCs research is beginning – the NIH should lead an effort to develop and implement a data sharing repository, as has been established by the NIH for autism, mental health and other disorders.[475] Further, investigators funded by the federal government using RDC and collecting a minimum data set, should be required to import their data into this repository as it becomes available, and an Interagency Coordinating Committee should be responsible for analyzing and publishing data on a regular basis.

Epidemiological, Health Services & Economic Impact Studies

Healthy People 2020/2030 Initiative

Centers for Disease Control (CDC) | Agency for Healthcare Research and Quality (AHRQ) | Health Resources and Services Administration (HRSA) | Department of Veterans Affairs (VA) | Department of Defense (DoD) | Centers for Medicare & Medicaid Services (CMS) | Health Insurers

Each of the COPCs addressed in this white paper have different numbers of published epidemiological and cost studies, estimating their impact on our nation's health and economy. However, one cannot simply add the prevalence and cost of each to delineate their cumulative impact. Epidemiological research on incidence, prevalence and shared risk factors associated with the development of COPCs, as well as health services research, in population-based samples is urgently needed to delineate the prevalence of multiple conditions, rates of overlap in different populations and the economic impact of having multiple conditions on the individual, payer and U.S. economy. As part of the Healthy People 2020/2030 Initiative, questions on COPCs should be added to national survey instruments used by the CDC's National Center for Health Statistics, and be administered annually to obtain baseline information and track progress over time.

Given the widespread prevalence of COPCs, and demonstrated risk factors common to military professionals, such as deployment, mood disorders and brain injuries, the DoD and VA should assess the prevalence, incidence, risk factors and cost of COPCs in both the active duty and retired military population. Wherever appropriate, COPCs should be included and incorporated into existing research programs on chronic pain, such as PASTOR PROMIS. (PASTOR is a DoD program and stands for Pain Assessment Screening Tool and Outcomes Registry. The DoD and NIH are collaborating on this joint initiative utilizing PROMIS, i.e., Patient Reported Outcomes Measurement Information System). Further, the agencies should work collaboratively with the NIH and other agencies to develop Research Diagnostic Criteria, a Common Data Elements Program and data-sharing repository, and require funded investigators to import a minimal data set.

Advancing Therapeutic Development

Food and Drug Administration (FDA) | Industry

Over the last two years, the FDA has undertaken an initiative to advance drug development to treat the symptoms of ME/CFS, including the creation of an industry guidance document to assist sponsors in the development of ME/CFS drug products.[476] Given the widespread prevalence, high rates of overlap and use of similar drug treatments across these conditions, the FDA should initiate a similar effort to advance both drug and non-drug treatments for COPCs that involves the patient community, clinicians treating COPCs and scientists studying these conditions.

Awareness and Educational Campaigns

Centers for Disease Control (CDC) | Health Resources and Services Administration (HRSA)

The CDC, with support from and in collaboration with other federal agencies and other stakeholders (e.g., patients, advocacy organizations, clinicians), should launch a multi-year awareness campaign that will educate the public about the seriousness and societal costs of COPCs; make available and promote sources of reliable information on the symptoms, diagnosis and treatments of COPCs; and provide information on effective communication strategies for patient-provider relationships. Further, using the latest scientific information on the diagnosis, treatment and prevention of COPCs, CDC and HRSA, in collaboration with other federal agencies, should support a multi-year campaign to better educate health care professionals, particularly primary care providers. The campaign should include the development of continuing medical education courses for professionals in practice, as well as curricula for medical, nursing and other allied health training programs.

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