July 31, 2024

National Institutes of Health
Request for Information on the Helping to End Addiction Long-term (HEAL) Initiative's Strategic Plan
National Institute of Neurological Disorders and Stroke (NINDS)
Notice Number: NOT-NS-24-106

The U.S. Pain Foundation is grateful for the opportunity to respond to the Request for Information from the National Institutes of Health (NIH) regarding the future of HEAL research priorities in pain management. The U.S. Pain Foundation is a national 501(c)(3) organization dedicated to supporting people living with chronic pain arising from various diseases, conditions, and serious injuries. The organization's mission is to connect, support, educate, and advocate for individuals with chronic pain, as well as their caregivers and health care providers.

Gaps in the Research Portfolio or Other Topics Not Previously Explored in HEAL Research

Population Health Research on Chronic Pain

Chronic pain and high-impact chronic pain are a tremendous disease burden on the American population and the U.S. economy in terms of patient suffering, loss of productivity, and the costs of health care and disability. Yet, the impact of pain is still largely unrecognized not only by the general public but by high-level policymakers who should have the data necessary to take action to improve care. Why?

The U.S. Pain Foundation, a patient organization with a mailing list of 34,000 and a social media following of over 230,000, believes that this is mainly due to the lack of comprehensive analysis and reporting on population-level health data related to chronic pain, as compared to other major diseases and conditions such as cancer, heart disease, diabetes, and substance use disorder.

Fortunately, because of efforts by NIH and OASH's Healthy People 2030 effort, the two questions on pain included in the National Health Interview Survey have yielded accurate data on the number of American adults with chronic pain - 20.9% or 51.6 million and high-impact chronic pain - 6.9% or 17.1 million. [1] But this is not enough.

Beyond these high-level prevalence numbers and some demographic data released last year, we lack comprehensive data on chronic pain in general, and on specific known pain conditions — such as incidence, risk factors, diagnosis and progression markers, detection, management and treatment, consequences, effectiveness of evidenced-based treatments, utilization of medical and social services, direct and indirect costs, and incidence and prevalence of co-occurring conditions such as anxiety, depression, and other pain or medical conditions. High-quality population health data is necessary to identify trends, risks, and consequences of pain, and to inform interventions aimed at improving care and patient outcomes while reducing costs to the U.S. health care system. Data like this will help in innumerable ways, such as by pinpointing disparities so we can focus resources where they are most needed, identifying who is at risk for chronification and the development of co-occurring conditions, developing more individualized and tailored treatment plans, and so much more.

[1] https://www.cdc.gov/mmwr/volumes/72/wr/mm7215a1.htm

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While NIH has not taken a lead role in analyzing and reporting on population health data on pain and has largely ceded this research domain to the Centers for Disease Control and Prevention, it is abundantly clear that CDC's Injury Prevention division that manages all of CDC's pain work, as well as CDC's overdose prevention surveillance system, does not have the funding, expertise, or interest in conducting this important work. The pain community ***needs*** NIH to take a lead role in this essential area of pain research if we are to make the kinds of strides necessary to improve the care of Americans living with pain.

Research on Peer-Support Groups in Managing Life With Chronic Pain

Another key area that we see as a gap in pain research at NIH is the investigation of the value of peer-led support groups and their role in helping individuals with chronic pain better manage their pain and cope with the challenges of living with high-impact chronic pain.

For nearly a decade, U.S. Pain has offered a national network of monthly peer support groups facilitated by individuals living with pain. These facilitators have undergone a comprehensive leader training program that uses curriculum developed by U.S. Pain. Volunteer peer leaders receive continuous support and guidance from our Director of Mental Health and Support to ensure their confidence and success in leading their groups, which focus on support and connection, while also incorporating evidence-based education.

Individuals in our groups receive education on such topics as pain tracking, pacing and limit-setting, building resilience, navigating grief and loss, self-compassion and self-care, mindfulness, acceptance, and other topics. We have seen the power of our groups in countering the isolation and loneliness of chronic pain, validating the experience of living with daily pain, and helping individuals cope with the enormous stigma that accompanies life with pain. Receiving feedback and guidance from others with similar experiences — and from a leader who also lives with chronic pain and understands what they are going through can be transformative.

HEAL pain researchers should look to members of the OUD/SUD community who have recognized the power of peer-led recovery groups — and even formalized the role of recovery coaches — to educate and support individuals struggling to regain their lives after the devastation caused by addiction. While chronic pain and opioid use disorder are different conditions, they have important characteristics in common — they are both lifelong chronic conditions that are often all-consuming and devastating. We urge HEAL researchers to investigate the benefits of peer-led pain support groups, and to study the role of recovery coaches and the less formalized pain coaching training programs as a possible model for more formalized chronic pain coaches in the future.

Research on Chronic Pain Across the Lifespan with Emphasis on Elderly and Pediatric Pain

Chronic pain research across the full lifespan — particularly in children and the elderly — has not been thoroughly explored. These specific groups face unique challenges in pain management that require focused research to improve their quality of life and health outcomes.

For example, children with conditions such as complex regional pain syndrome (CRPS), juvenile arthritis, migraine disease, and many others not only experience physical pain but also undergo significant disruptions in their social and academic lives. A systematic review by Tutelman et al in 2021 reported that chronic pain affects 11-38%[2] of children and adolescents (the breadth of this range is another indication

[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7888311/

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that additional targeted research on pediatric pain is needed). Many of these youth report pain-related interference with school activities and social interactions, leading to long-term psychosocial challenges and developmental delays. Children also are frequently undertreated for chronic pain due to misconceptions about their pain tolerance and concerns about the side effects of pain medications. Many families encounter providers who are not receptive to, or trained in, the concept of pediatric chronic pain at all.

There is an urgent need for research to develop age-appropriate assessment tools and pain management strategies, including non-pharmacological interventions and support systems tailored to children's developmental stages. Understanding the ways in which pediatric chronic pain can present, as well as the psychosocial impact of chronic pain on children — including its effects on academic performance, social interactions, and mental health — is crucial to provide comprehensive care and improve their quality of life.

In the elderly population, chronic pain is prevalent, due in part to age-associated conditions such as osteoarthritis, back pain, diabetes-related neuropathy, and cancer. NIH estimates that 50% of older adults[3] live with chronic pain, significantly impacting their mobility, independence, and mental health. This demographic is more likely than younger adults to encounter health care professionals who believe pain is an unavoidable aspect of aging that does not merit targeted pain management treatments. Additionally, elderly individuals frequently experience post-surgical pain from musculoskeletal procedures and joint replacements, yet research on optimal pain management strategies for this demographic remains scarce. Chronic pain in older individuals often leads to increased rates of depression, anxiety, and social isolation, exacerbating the overall health decline in this vulnerable group.

Research should focus on the effectiveness of various pain management approaches specifically targeting older adults — including pharmacological treatments, physical therapy, and integrative medicine — to enhance functional outcomes and quality of life for these individuals. Moreover, understanding the intersection between chronic pain and aging-related psychosocial challenges, such as isolation, depression, and cognitive decline, is vital for developing holistic care models that address both physical and emotional health.

The disparity in research focus on pediatric and geriatric pain management highlights a critical gap that needs attention. It is important for NIH to prioritize and fund comprehensive research initiatives that explore the specific experiences and needs of children and the elderly affected by chronic pain. By advancing our understanding of the characteristic conditions and psychosocial challenges these age groups face, we can develop more effective, age-appropriate pain management strategies, alleviating suffering and enhancing overall well-being and life satisfaction.

Enhanced Focus Needed on Priorities for Pain Research

Development of Novel Non-Addictive Therapeutics

In 2018, one of the main reasons Congress agreed to invest nearly half of HEAL funding in pain research was to discover and develop novel, non-addictive pain therapeutics. It has been six years, *and over $1 billion of investment in pain research*, and we are still waiting for a novel pain therapeutic developed with NIH HEAL funding to come through the pipeline and reach patients. We urge NIH HEAL leaders and

[3] https://magazine.medlineplus.gov/pdf/MLP_Fall_11.pdf, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6658091/

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researchers to maintain the focus on novel therapeutics for pain as the number-one research priority of the pain community.

The need for new, non-addictive pain medications for the millions of Americans whose lives have been devastated by chronic pain has perhaps never been greater or more urgent — especially for those suffering with high-impact chronic pain. Over the past eight years, the response to the opioid crisis has caused a precipitous drop in opioid prescribing rates, with millions of Americans force-tapered or removed from opioid treatments with extremely limited or no other effective therapeutic options to replace them. And while we are strong believers in multidisciplinary pain care, including non-pharmacological therapies, individuals with the most severe chronic pain typically need medications to control their pain alongside other modalities and strategies, such as some form of movement, pacing, and psychological support.

In 2022, U.S. Pain conducted a comprehensive survey to better understand the challenges faced by those living with chronic pain, the treatments they have tried, and the barriers they have faced in finding effective care. A total of 2,275 individuals living with chronic pain responded: 99% said pain has restricted their ability to engage in routine daily activities, while 71% consider themselves disabled by pain. More than half (52%) of respondents reported having an average pain level of 7 or more, and only 18% are employed full time.

Most respondents (79%) take prescription medications for their pain. Those surveyed felt that pharmacological treatments are the most effective treatments available to them — 77% using prescription medications said that medication is the most helpful treatment for their pain, and 24% of respondents said that no side effect would prevent them from trying a medication to manage pain — but the quality-of-life numbers above show that for these individuals' pain remains inadequately managed. Indeed, the top policy priority for respondents was wanting new medications for chronic pain.

These responses paint a troubling picture that should compel the efforts of HEAL: High-impact chronic pain is poorly managed with the armament of medication available today, even though it is the best treatment we have; and patients are so desperate for novel therapeutics that they would try new medications for their pain regardless of their side effects.

There is no question that successful discovery and development of novel pain therapeutics has long been and remains an extremely challenging endeavor with several notable failures. A February 2023 report[4] by the Biotechnology Innovation Organization (BIO) found that pain remains a vastly underfunded therapeutic area relative to its prevalence and impact. Excluding drugs for migraine, there have been no therapeutics with novel targets approved in the past five years. A key takeaway from the BIO study was that "clinical success in pain drug development remains extremely difficult for novel drugs, with only a .7% probability of FDA approval from Phase I compared to an overall 6.5% success rate for novel drug programs across all diseases." The same report found that Phase III success rates were lower than all major disease categories. Only one in five novel pain drugs progressed to a New Drug Application (NDA) or Biologic License Application (BLA) filing stage.

[4] https://go.bio.org/rs/490-EHZ-999/images/BIO_The_State_of_Innovation_in_Pain_and_Addiction_2017_2022.pdf

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The directors and senior management of the NIH HEAL pain program have done an excellent job collaborating with scientific entrepreneurs to advance new molecules through Phase I. NIH has provided funding at crucial stages, offered advice, and shared business expertise. However, NIH should take further steps to advance promising therapeutics into Phase II and III. This could involve hiring consultants to guide developers in designing novel clinical trials, funding research for better tools to measure pain in trials, and engaging in discussions with the FDA's pain medicine division to expedite the development of promising pain therapeutics.

Biomarkers

The discovery and validation of objective, measurable signatures of chronic pain would be enormously beneficial for patients, providers, developers of novel treatments, and researchers. From a patient perspective, the invisible, subjective nature of chronic pain prolongs the interminable struggle to reach a diagnosis, invalidates the individual's suffering, often causes health care providers to doubt, dismiss, and demean the patient's experience, and frequently leads to denials of disability determinations — despite a patient's inability to work and financially support themself and their family due to their level of pain.

Providers of patients presenting with chronic pain with no visible or diagnostic evidence of impairment such as an X-ray of a broken bone often have to rely on subjective self-reports and clinical impressions. At best, these impressions are imprecise and leave providers in the dark about appropriate treatment selection, and at worst, they can create a tense or fraught physician-patient relationship that leaves the patient feeling disbelieved, dismissed, and stigmatized.

The absence of identified, objective measures of pain is a significant obstacle in successfully reaching the market with novel pain therapeutics. Currently, therapeutic trials primarily rely on a significant change in the rudimentary 0-10 Numeric Pain Rating Scale as the main endpoint. However, having validated and reliable biomarkers to measure patient response to treatment would substantially accelerate the development of novel treatments for patients.

We are aware that NIH HEAL has made significant progress in identifying promising pain biomarkers, including neuroimaging, functional MRI, blood gene expression, and others. However, it is crucial to prioritize this work so that new pain measurement tools can be employed in drug discovery and clinical practice.

How Acute Pain Turns Chronic

It would be difficult to overstate how critical it is for us to gain a thorough understanding of the transition from acute to chronic pain — when a healthy, adaptive process turns into a maladaptive, tortuous existence for millions of Americans. Chronic pain often persists over a lifetime for its victims, significantly diminishing their quality of life and imposing a substantial economic, social, and emotional burden on people with chronic pain and their families. While there has been progress in understanding the complex pathophysiology underlying this transition in the peripheral and central nervous systems, as well as ongoing efforts to determine potential risk factors that would make these processes more likely to occur, we believe it is imperative for NIH to continue to focus research efforts in this area.

Writing in JAMA Network Open Neurology in May 2023, NIH's Richard Nahin and colleagues found the incidence or number of new cases of chronic pain to be higher than other major chronic diseases in the U.S. such as diabetes, depression, and hypertension. This was a rare longitudinal population-based study of pain

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and points to the great need, as we discussed in our first research gap recommendation above, for better population-level data on chronic pain, including more robust longitudinal studies. This study also only looked at a one-year increment, so it may be the tip of the iceberg regarding a concerning trend of annual increases in the number of new cases of chronic pain.

Clearly, there is an urgent need to identify possible biological and psychosocial factors that might make certain individuals more susceptible to developing chronic pain. We are hopeful that the Acute to Chronic Pain Signatures (A2CPS) program underway will help accomplish this. We urge further research as well into preventive intervention strategies that can be implemented early in the treatment of acute pain (or even before its onset, in the case of surgery), to reduce its progression to chronic pain.

Patient-Centered Research: Persons With Lived Experience Should Play a More Central Role in Research Focus Area Teams

The U.S. Pain Foundation applauds NIH HEAL for its important, comprehensive effort in developing a strategic plan for the pain research portion of HEAL. We believe this is an excellent time for NIH to reconsider the involvement of individuals with lived experience in the research process. Instead of the previous approach of having an adjunct patient advisory board, we recommend making this strategic planning process truly "patient-centered" by including a person with lived experience on each of the focus area teams creating the strategic plan.

While NIH may be able to find persons with lived experience who are also scientists engaged in research to join these focus area teams, we encourage NIH to offer some basic neuroscience education and guidance to individuals with lived experience who would like to participate so that more patients can be involved. It is our experience and view that patients' participation as partners and collaborators — individuals who have years of experience living with a chronic condition, trying numerous treatments, interacting with health care providers and other individuals with pain, and navigating the complexity of our health care delivery system — will bring invaluable contributions to the focus area teams.

Comments on Additional Areas of Interest NIH Identified in RFI Announcement

Opportunities to Advance Health Equity in the Treatment of Pain for all People

Advancing health equity in pain management is crucial to ensure that all individuals, regardless of their background, receive the care and support they need. One significant challenge is the disparities faced by BIPOC (Black, Indigenous, and People of Color) individuals, as well as individuals from lower socioeconomic backgrounds, in accessing pain management. Studies show that these groups are often undertreated for pain due to biases and misconceptions held by health care providers. For example, CDC highlights that Black individuals are less likely[5] to receive opioid prescriptions or are prescribed lower doses compared to their white counterparts, even when presenting with the same level of pain. This inconsistency extends to the overall quality of pain management care, which can lead to worsened health outcomes and increased suffering.

Bias and misconceptions around the use of pain medicines further complicate the treatment landscape for marginalized groups. There is a pervasive stereotype that BIPOC individuals are more likely to misuse pain medication, which influences prescribing behaviors and leads to inadequate pain relief. Additionally,

[5] https://www.cdc.gov/mmwr/volumes/71/rr/rr7103a1.htm

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individuals from lower socioeconomic statuses, as well as rural residents, often lack access to comprehensive pain management resources, including non-pharmacological treatments and specialized or holistic care. This challenge is exacerbated by systemic issues such as lack of insurance coverage, transportation barriers, work or childcare obstacles, and lower health literacy — all contributing to a cycle of untreated or poorly managed pain.

LGBTQ+ individuals also encounter unique barriers in seeking effective pain management. They often face discrimination and stigma in health care settings, leading to mistrust and reluctance to seek care. This community also deals with higher rates of chronic pain conditions, yet has limited access to knowledgeable and culturally competent health care providers.

These biases and the lack of tailored pain management strategies for these groups highlight the urgent need for policies and programs that promote equitable pain management practices. Addressing the stereotypes and misconceptions that contribute to substandard pain treatment for these populations is a vital step in developing and equitably utilizing non-addictive pain management medications, treatments, and therapies. Implementing bias training for health care providers, improving access to diverse pain management resources, and ensuring culturally competent care are essential steps to address these disparities and improve health outcomes for all individuals experiencing pain.

Opportunities for Research on the Optimal Role and/or Effectiveness of Opioids in Long-Term Treatment and Management of Chronic Pain

The publicity and hype surrounding opioid medications have prevented an unbiased, rational study of the optimal role and effectiveness of opioids in the long-term treatment and management of chronic pain.

Research has mainly focused on the risks of addiction and overdose, overshadowing the real-life experiences of individuals with chronic pain who benefit from opioid therapy. It would be beneficial for NIH to conduct studies that capture the full range of outcomes for patients on long-term opioid therapy, including those who have maintained a high quality of life and functional status. Failing to do so has led to policies that, though well-intentioned, have inadvertently caused significant harm to people with chronic pain.

The precipitous drop in opioid prescribing over the past eight years has left many patients struggling with unmanaged pain — resulting in devastating consequences for countless individuals that go unnoticed due to the lack of formal documentation of the impact of this reduction. While there is extensive discussion on overdose deaths, there is a noticeable lack of focus on the suicides resulting from mismanaged pain. We urge NIH to invest in research that documents these outcomes, assesses the real-world impacts, and provides a comprehensive understanding of the impact of opioid restrictions on the chronic pain community.

Research Needed to Address Pathways to Care for Individuals with Chronic Pain and Comorbid Psychiatric Disorders

Research is needed to address the complex relationship between chronic pain and comorbid psychiatric disorders in order to improve the quality of care for individuals dealing with these conditions.

Chronic pain often coexists with mental health conditions such as depression and anxiety, which can worsen pain and vice versa, creating a challenging cycle that complicates treatment. A deeper

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understanding of these interactions can help dispel the misconception that pain is "all in your head" while still acknowledging its mental health effects, and promote more effective, comprehensive treatment approaches.

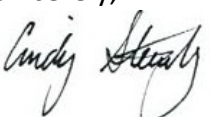
In addition, advancing research to clarify the pathways between chronic pain and mental health conditions could shed light on the "chicken-and-egg" dilemma often observed in these cases. This could involve studying genetic, neurobiological, and psychosocial factors that contribute to the onset and progression of these comorbid conditions. By conducting longitudinal studies and integrating data from diverse populations, researchers can identify common biomarkers and risk factors, ultimately leading to more personalized and precise interventions.

Given that an estimated 50% of people[6] with chronic pain experience depression and anxiety, it is crucial to prioritize research that can lead to comprehensive care models addressing both pain and mental health simultaneously. Such efforts will not only improve patient outcomes but also reduce the stigma and misconceptions associated with chronic pain and its psychological impacts.

In Conclusion

We hope NIH will give our recommendations serious consideration as it moves forward with this important work that represents hope to so many who are suffering with debilitating chronic pain. Should we be able to provide additional information or assist with NIH's efforts in any way, please feel free to contact me using the information listed below.

Sincerely,



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[6] https://www.apa.org/monitor/2024/03/chronic-pain-depression-anxiety