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Focus Article

Research Agenda for the Prevention of Pain and Its Impact: Report of the Work Group on the Prevention of Acute and Chronic Pain of the Federal Pain Research Strategy

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Abstract: **After the 2011 Institute of Medicine report on chronic pain, the Interagency Pain Research Coordinating Committee (IPRCC) was created to enhance research efforts among federal agencies. The IPRCC and Office of Pain Policy at the National Institutes of Health collaborated to identify gaps in knowledge and address them via a Federal Pain Research Strategy (FPRS). Interdisciplinary work groups (WGs) were established to make research recommendations in 5 areas: prevention of acute and chronic pain, acute pain and acute pain management, transition from acute to chronic pain, chronic pain and chronic pain management, and disparities in pain and pain care; cross-cutting issues were also considered. The objective was to provide guidance on current research and to make recommendations about addressing identified gaps. Findings from the Prevention of Acute and Chronic Pain WG are summarized in this article. The WG created subgroups to develop recommendations on specific aspects of prevention of acute and chronic pain, including: public education, primary prevention, secondary prevention, tertiary prevention, transition from acute to chronic pain, and cross-cutting mediators. No formal literature review was conducted; however, external advisors were available and consulted as needed. Seven key research priorities were identified. The one deemed "greatest near-term value" was to optimize public health strategies to educate patients on managing pain; that deemed "most impactful" was to determine an association between patient and intervention factors. Other recommendations were related to the epidemiology of acute pain from health care procedures, the epidemiology of acute pain from work-related injuries, safety and effectiveness of management of pain associated with health care procedures, optimizing approaches to acute postsurgical pain, and safety and effectiveness of early interventions for tertiary prevention. Stakeholders, including federally sponsored research programs, researchers, health care providers, policy makers, patients, and others should work together to implement recommendations and address important gaps.**

From the National Institutes of Health and Interagency Pain Research Coordinating Committee (www.iprcc.nih.gov). Other committee members: Anthony Delitto, Cathy Glaser, and Ruth Grunau.
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Perspective: ***The FPRS Steering Committee created 5 WGs to identify research needs and make recommendations in key areas of research. This article reports the results of one—the Prevention of Acute and Chronic Pain group. Several research priorities emerged, and recommendations made to fill existing knowledge gaps.***

Key words: *Federal pain research strategy, interagency pain research coordinating committee, acute pain, chronic pain, pain prevention, interdisciplinary research, research priorities.*

The Patient Protection and Affordable Care Act instructed the Department of Health and Human Services to work with the Institute of Medicine to examine the impact of pain on public health in the United States.[98] The Institute of Medicine reported that chronic pain affected 100 million adults in the United States, at an estimated annual cost of $635 billion for medical interventions and lost productivity.[67] The report identified numerous challenges in the current approach to managing pain and recommended that federal agencies develop a plan to improve this landscape.[67] In response, the federal government created the Interagency Pain Research Coordinating Committee (IPRCC) to enhance pain research efforts among federal agencies, including the Centers for Medicare and Medicaid Services, National Institutes of Health (NIH), Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Food and Drug Administration, Department of Defense, Veterans Health Administration, and others.[98]

To guide their efforts, the IPRCC and Office of Pain Policy at the NIH collaborated to identify critical gaps in knowledge related to pain and then address them through a strategic, long-term, Federal Pain Research Strategy (FPRS).[68] The FPRS Steering Committee included representatives from the IPRCC, federal agencies (eg, NIH, health care providers [HCPs]), scientists with expertise in pain research, and other interested stakeholders (eg, patients with chronic pain).[68] Fig 1 provides an overview of this genesis. The FPRS Steering Committee then created 5 work groups (WGs) to identify research recommendations in 5 key areas of pain research: 1) prevention of acute and chronic pain, 2) acute pain and acute pain management, 3) transition from acute to chronic pain, 4) chronic pain and chronic pain management, and 5) disparities in pain and pain care.

Each WG consisted of 12 to 15 members with a variety of backgrounds, including HCPs from different professions and specialties relevant to pain research, academic researchers with experience in basic or applied pain research, and patient advocacy group representatives. WGs were assisted by representatives from the NIH and instructed to develop a small number of priority research recommendations that could be incorporated into the FPRS and implemented by federally funded research programs. The objective of this article is to summarize findings from the FPRS WG on the Prevention of Acute and Chronic Pain.

Process

The WG met regularly via teleconference from early 2016 to mid-2017 to develop its recommendations. The WG began by discussing the concept of pain prevention, which was quite challenging because it could be

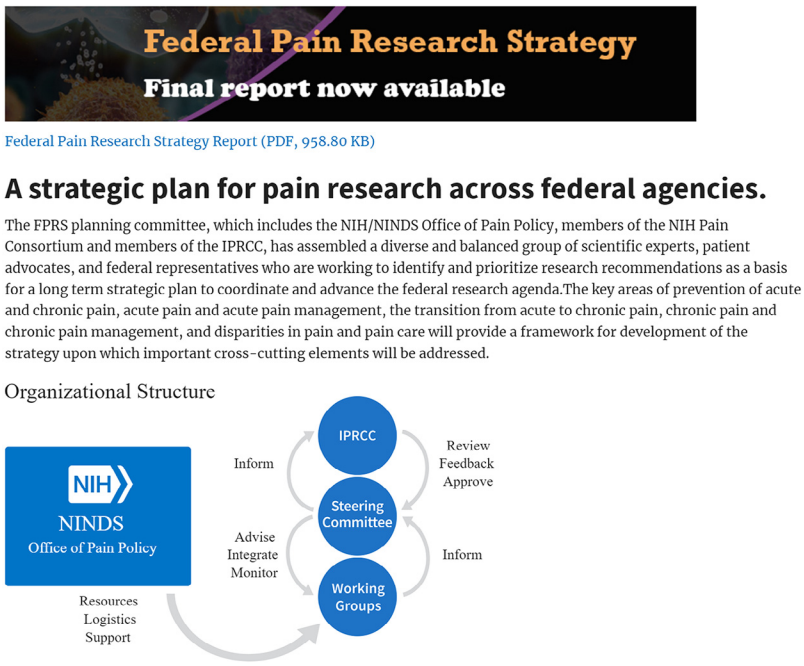

Figure 1. Overview of components of the FPRS. (From: https://iprcc.nih.gov/Federal-Pain-Research-Strategy/Overview)

Table 1. Most Impactful Priorities (Selected Within Each FPRS WG) of Those in Our WG*

Prevention of Acute and Chronic Pain*	Determine association between patient and intervention factors and psychosocial interventions
Acute Pain and Acute Pain Management	Heterogeneity of the circuitry involved in acute pain sensation and modulation
Transition from Acute to Chronic Pain	Understand and address plasticity mechanisms that promote persistent pain and (endogenous) resolution mechanisms that may reverse persistent pain
Chronic Pain and Chronic Pain Management	Determine the mechanisms that sustain or resolve chronic pain and which of these elements can be intrinsically and extrinsically modulated
Disparities in Pain and Pain Care	Investigate biological, psychological, social mechanisms that contribute to population group differences in chronic pain

*Also public health strategies to educate patients on managing pain, epidemiology of acute pain from HCPs, safety and effectiveness of opioid-sparing, multimodal pain management, predictor variables of persistent and/or recurrent pain, optimize postsurgical approaches for acute pain, effectiveness of early intervention for tertiary prevention, optimal therapies for tertiary prevention, patient factors, intervention factors, psychosocial interventions associated with outcomes, and epidemiology of transition from acute to chronic pain.

approached from different perspectives and could extend far beyond the desired scope (eg, pain from motor vehicle collisions could conceivably be prevented by improving road safety to avoid crashes). After discussing a variety of approaches to this task, the WG elected to create subgroups that would focus on the specific aspects of prevention of acute and chronic pain that seemed most relevant and addressable through additional research. A public health perspective was adopted, applying the concepts of primary prevention (ie, preventing a condition from ever occurring), secondary prevention (ie, preventing a condition that has already occurred from worsening), and tertiary prevention (ie, mitigating the impact of a chronic condition on overall health and well-being) to the topic of pain prevention. In this context, the primary prevention of pain was interpreted by the WG as the prevention of acute pain, whereas secondary prevention was interpreted as the prevention of chronic pain when acute pain occurred, and tertiary prevention was interpreted as mitigating the impact of chronic pain on overall health and health-related quality of life. Three additional subgroups were also formed to focus on the role of public education in pain prevention, the transition from acute pain to chronic pain, and cross-cutting issues relevant to multiple subgroups.

Each of the 6 subgroups then identified perceived gaps in the scientific literature in their area of focus, how that gap impeded the goal of preventing pain, and the feasibility of addressing gaps through research; no formal literature review was conducted, but external advisors were consulted by the subgroups as needed. Subgroups proposed 5 to 10 recommendations to the broader WG and discussed them until 3 to 5 key recommendations emerged by consensus. Draft findings from all FPRS WGs were presented at a public meeting in June 2017, and feedback was solicited from the public. Each WG then selected one of their recommendations as being "most impactful" (ie, addressing this gap would have the greatest impact on pain; Table 1), and one as being of "greatest near-term value" (ie, research on this topic is ready to move forward now with additional resources; Table 2). In addition, members from all FPRS WGs reviewed recommendations from all the other WGs and scored them on the basis of perceived importance; recommendations scoring in the highest quartile were deemed of "top priority" (Table 3). The FPRS issued its final report in October, 2017. Tables 1, 2, and 3 show the prioritized research recommendations from all FPRS WGs, including the Prevention WG.

The purpose of this article is to further discuss the recommendations of our FPRS WG on the prevention of acute and chronic pain.

Public Education About Pain Prevention

Pain is often responsible for health care utilization that is of limited value because all painful conditions are negatively affected by personal behaviors, lifestyle factors, and comorbid disorders that contribute to chronicity, morbidity, and disability.[129] Public education is therefore required to heighten awareness about pain and its health consequences, improve public knowledge about strategies that individuals can use to manage their own pain, and address disparities that exist in the experience of pain among subgroups of Americans.

Table 2. Greatest Near-Term Value Priorities (Selected Within Each FPRS WG)

Prevention of Acute and Chronic Pain*	Optimize public health strategies to educate patients on managing pain
Acute Pain and Acute Pain Management	What are the cellular mechanisms of heterogeneity in acute pain sensation?
Transition from Acute to Chronic Pain	Understand and address plasticity mechanisms that promote persistent pain and (endogenous) resolution mechanisms that may reverse persistent pain
Chronic Pain and Chronic Pain Management	Determine optimal safe and effective chronic pain management
Disparities in Pain and Pain Care	Better define the epidemiology of pain in disparate populations, including children, women versus men, specific racial and ethnic groups, older adults, and socioeconomically disadvantaged people

*Other one same as in Table 1.

Table 3. Top Priorities (Highest Quartile Scores Across All FPRS WGs)

Develop safer opioids, new, nonopioid analgesics, and the first generation of disease-modifying agents
Develop a research network
Develop, evaluate, improve models of pain care
Develop approaches incorporating principles of precision medicine to prevent and effectively treat chronic pain
Prospective studies for susceptibility and resilience factors underlying the transition from acute to chronic pain (eg, formalizing individualized treatment recommendations on the basis of risk factors)
Understanding and addressing plasticity mechanisms that promote persistent pain and (endogenous) resolution mechanisms that may reverse persistent pain
Mechanistic trials of risk and resilience to chronic pain with meaningful outcome measures
Determine the mechanisms that sustain or resolve chronic pain and which of these elements can be intrinsically and extrinsically modulated
Determine optimal safe and effective chronic pain management
Determine optimal approaches for use of self-management strategies in chronic pain
Determine the bidirectional relationship between common comorbidities and chronic pain
Understand mechanisms of childhood chronic pain
Investigate biological, psychological, and social mechanisms that underlie the development and persistence of chronic pain in disparate populations

Awareness About Pain and Its Health Consequences

The public needs better information about the prevalence, risk factors, and consequences of pain-related conditions throughout their lives, to encourage informed decisions about the importance of healthy lifestyles that promote exercise, nutrition, stress management, self-care, and appropriate health care-seeking for painful conditions. Ideally, such information would be standardized for common pain conditions; the NIH Task Force on Research Standards for Chronic Low Back Pain[41] serves as a model for establishing meaningful case definitions and metrics to inform future research efforts.

Information to Guide Appropriate Care-Seeking

Numerous approaches to managing pain are available, ranging from self-care to primary care, emergency care, specialty care, as well as complementary and integrative medicine. These interventions may include medications, injections, surgery, physical therapy, behavioral health interventions, and complementary and integrative health approaches, each with varying levels of evidence with respect to their benefits.[27,28,104] Research is needed to inform the development of therapeutic algorithms, and how treatments affect the natural history of pain. Research should also assess how psychosocial factors (eg, pain catastrophizing,[119] self-efficacy[94]) affect chronicity and disability related to pain, and how education can affect these factors.

Public Health Strategies to Educate Patients on Managing Pain

Public education about pain should include biological as well as psychosocial aspects of pain, and emphasize self-help strategies to prevent, cope with, and reduce the impact of pain. Such research should also explore the use of technology, social media, and social marketing techniques to address misconceptions about pain and factors that exacerbate its societal impact.[22,58,67] Investigations are needed to develop materials and methods targeted at the public, individuals with pain, and HCPs, as well as assess the effect of health literacy, health-seeking behavior, and shared decision-making on the effectiveness of those education approaches.[6]

Disparities in the Experience of Pain and Its Consequences Among Subgroups

Although everyone is at risk of experiencing pain, certain subgroups may be disproportionately predisposed to, and affected by, pain and related disability for a variety of reasons (eg, occupational, environmental, geographic); public education efforts should be tailored to address relevant subgroups.[131] Research should emphasize the importance of education about safety in the home environment, recreational and sports activities, workplace, community environment, transportation, and residential facilities, and identify populations at risk for slips, falls, and accidents (eg, elderly) that may benefit most from prevention efforts. Further research is also needed on public education to prevent chronic pain in the elderly, and those with multiple comorbidities (eg, diabetes, heart disease, depression)[13,120] to help maintain their independence and minimize pain-related disability (see the FPRS Disparities WG at www.iprcc.nih.gov for further discussion and recommendations on this topic).

Primary Prevention of Pain

The primary prevention of pain is a broad concept that can encompass safe behaviors (eg, seatbelt use), disease prevention (eg, immunizations), injury prevention (eg, ergonomics), health promotion (eg, smoking cessation, exercise, weight control), prevention of excessive pain from common health care procedures (eg, inoculations, postsurgical pain), and management of recurring painful episodes (eg, sickle cell crises, migraines), among others. The success of these approaches can be influenced by a variety of behavioral, environmental, genetic, neurophysiological, contextual, and psychosocial factors. In

Table 4. Interacting and Interrelating Factors

Predisposing/Precipitating	*Perpetuating/Protective/Alleviating*	*Contextual*
• Genetics • Environment • Demographic characteristics • Previous learning history • Lifestyle (smoking, diet) • Physical trauma • Disease/illness • Emotional trauma	• Symptoms • Attitudes/beliefs • Meaning • Coping repertoire • Social support • Financial resources • Behavioral responses • Consequences	• Biopsychosocial versus biomedical perspective • Individual and contextual variability (eg, taking into account different strengths/interactions array biological, psychological, and social factors across individual patients

particular, 3 sets of interacting and synergistic factors have been identified in the development and chronicity of pain: 1) predisposing/precipitating (eg, genotype, environment, demographic, lifestyle, disease, physical trauma, emotional trauma, 2) protective, alleviating, and perpetuating (eg, symptoms, attitudes and beliefs, social and financial supports, behavioral responses),[47] and 3) contextual (Table 4). Each is further discussed in the following sections.

Predisposing/Precipitating Factors

A proposed framework is best appreciated by taking a longitudinal, rather than a cross-sectional, perspective because factors can change over time. For example, age is a predisposing factor for the development of osteoarthritis, but can also become a precipitating factor for the onset of osteoarthritis, and then a perpetuating factor for osteoarthritis when older age is associated with reduced physical activity and social isolation. The role of age and other factors in the development and chronicity of pain and disability can change depending on when they are assessed (eg, before, at onset, or long after onset), which should be explored further to develop effective programs to mitigate the effect of various risk factors.

The traditional biomedical model of pain, with its mind-body dualism, is inadequate because it does not explain: 1) differences in pain intensity and disability with the same physical pathology, 2) variability in treatment response by patients with the same physical pathology, 3) the persistence of pain in the absence of detectable physical pathology, and 4) variability in chronic pain responses for individuals with equivalent physical pathology. Although biological factors may initiate, maintain, and modulate physical responses to painful stimulus, psychosocial factors (eg, personality, current beliefs, expectations, mood) continually shape behavioral responses to pain. Conversely, psychosocial factors may also influence biology through hormone production,[90,92] brain structure and processes,[56,60,80,108] and the autonomic nervous system.[33,89,90]

Protective, Alleviating, and Perpetuating Factors

Behavior can also affect biology, such as when a person avoids certain activities to reduce symptoms,[35,127] leading to physical deconditioning, social isolation, and amplification of nociception. In addition, medications used to treat pain (eg, steroids, opioids) may affect concentration, fatigue, self-perception, and the ability to engage in certain activities, further "clouding" the role of individual factors whose importance may shift over time.[101,113] These medications can also produce negative side effects, such as constipation and hyperalgesia. Interventions aimed at only some of these 3 core factors (ie, biological, psychological, sociocultural) are less likely to succeed.

Individuals differ markedly in how they experience pain because they are not passively responding to a physical sensation, but seeking to make sense of it on the basis of their beliefs, attitudes, expectations, and history to determine if it requires attention or can safely be ignored, resulting in a uniquely constructed reality for each person experiencing pain. Pain is also filtered through individuals' genetic composition, and modulated by their physiological status, idiosyncratic appraisals, expectations, current mood state, and sociocultural environment.[43,47,53] A headache may thus be viewed by some as a minor inconvenience, but as a potential brain tumor or stroke by others. Although biological factors instigate the initial report of pain, psychosocial factors can be responsible for maintaining it by misinterpreting or overemphasizing symptoms. Beliefs, attitudes, previous learning experiences, as well as social, cultural, racial, and ethnic group membership, can also affect perceptions about the appropriate treatment of pain, when care is sought, from whom it is sought, and the patient-HCP relationship.[1,34,84,93] Research should further explore the role of these factors in health care-seeking for pain to help formulate individualized treatment recommendations and optimize outcomes.[47,100,113]

Contextual Factors

The biopsychosocial-contextual perspective focuses on disease as well as illness—which is influenced by a complex interaction of biological, psychological, and social variables—and views pain as neither solely physical nor solely psychological. Rather, pain is a complex amalgam maintained by an interdependent and inter-related set of biomedical, psychosocial, behavioral, environmental, and contextual factors whose relationships evolve over time. From this perspective, each of these factors contributes to pain, and it is the interactions among factors that produces the subjective experience of pain.[47,53]

Despite these advances in our knowledge about pain, current interventions aimed at preventing the onset, duration, and evolution of pain and disability are only

modestly effective at best.[123] This failure may be related to a focus in recent decades on asking yes/no questions as to whether interventions are effective, rather than considering how interventions can be most effective, when they should be used, for whom, compared to what alternatives, and which outcomes should be measured. Future research should attempt to address these questions to maximize the therapeutic effectiveness and cost-effectiveness of available interventions for the prevention of pain. An individualized, tailoring approach to each patient is needed, as now encouraged by the precision medicine approach.[4]

Individual and Context Variability

The conventional biomedical approach to pain often assumed that pain results from a specific, identifiable causal event that affects anatomy or physiology. Efforts to prevent pain were therefore on the basis of identifying directly observed physical and environmental factors and mitigating their effects through various structural interventions (eg, ergonomics). In those instances when the occurrence of pain cannot be prevented completely, efforts are often made to identify and address the organic dysfunction that arises as a result of pain (eg, acute inflammation). Such approaches fail to consider the wide variability in how individuals react to these factors, and assume that interventions will have a fixed (ie, mean) effect across the population, rather than acknowledging that only some individuals will respond positively. Research should examine the inter-relationships along physical, psychosocial, behavioral, and contextual factors in the development and prolongation of pain, while being cognizant that the role of these factors may change over time, and thus affect how they are incorporated into primary, secondary, and tertiary prevention of pain and related disability.

Secondary Prevention of Pain

Secondary prevention of pain refers to preventing the transition from acute pain to chronic pain, defined as a pain problem that has persisted for at least 3 months and has resulted in pain on at least half the days in the past 6 months.[30,40] Chronic pain can be disabling, lack a biological underpinning, and is incredibly costly to society. A 2-step approach is proposed to develop a research plan for the secondary prevention of pain that includes: identifying painful conditions with a high incidence of chronicity, and identifying research gaps in basic and applied sciences that need to be filled to prevent their transition to chronic pain. This is particularly important for vulnerable subgroups such as children, elderly individuals, racial and ethnic minorities, and individuals with disabilities (see the FPRS Disparities WG for further discussion and recommendations on this topic).

Conditions with a High Incidence of Chronic Pain

Acute pain from a variety of surgical procedures may transition to chronic pain, including laminectomy, spinal fusion, mastectomy, thoracotomy, joint arthroplasty, amputation, and surgical oncology. Pain from acute trauma associated with motor vehicle accidents, slips and falls, and other injuries is also at risk of transitioning to chronic pain. A broad range of chronic medical conditions include a high incidence of pain including common musculoskeletal (eg, low back pain, knee pain), neurological (eg, neuropathies), vascular (eg, migraines, peripheral arterial disease), and cardiac (eg, chest pain due to coronary heart disease) conditions, as well as complications from diabetes (eg, ulcers) and cancer (eg, bony metastasis). As symptoms persist, the acute phase transitions to become chronic and the set of integrated factors comprising the biopsychosocial model described previously come into play with the weight of the psychosocial and behavioral factors increasing.

Optimizing Variables Predictive of Persistent Pain

It is challenging to identify those with acute pain who have a higher risk of developing chronic pain and pain-related disability, because spontaneous recovery is the rule for most acute pain conditions. When chronic, pain can be disabling, costly, and difficult to manage for all stakeholders, including patients, HCPs, and payers. Because of the prevalence of many acute pain conditions (eg, low back pain), it is not feasible to apply comprehensive interventions aimed at preventing chronic pain in everyone. Research is therefore needed to determine accurate screening tasks identifying individuals with acute pain who are at greatest risk of developing chronic pain by addressing biological, psychological, and social risk factors to inform treatment selection and research. For example, identification of accurate biomarkers for chronic pain and response to analgesia could provide guidance to develop specific drugs that more effectively manage acute pain among those with a higher likelihood of transitioning to chronic pain.[12] Adopting screening tools for psychosocial risk factors (eg, catastrophizing, kinesiophobia) could promote a stratified approach to acute pain, whereby interventions are matched to risk factors. Future research could build on the concept of the STarT Back tool and approach to low back pain, and explore similar interventions for other acute pain conditions at high risk of transitioning to chronic pain.[48,63,115]

Optimizing and Exhausting Nonsurgical, Nonpharmacological Approaches to Acute Pain

Because chronic pain is recalcitrant to many interventions, it is imperative to optimize the management of acute pain in the short time frame available (ie, <3 months) to minimize its transition to chronic pain. Conceptually, this can be accomplished by using a variety of available interventions (eg, medications, rehabilitation, behavioral) to diminish acute pain as thoroughly and quickly as possible. However, evidence is currently lacking to support the optimal approach to managing acute pain

that could, in fact, prevent the onset of chronic pain. Clinical practice guidelines on managing acute pain encourage advice to "stay active" and "maintain a positive perspective on the prognosis," but these recommendations are unlikely to affect the trajectory from acute pain to chronic pain by themselves.[29,78] Research is therefore needed to develop comprehensive and cost-effective approaches to acute pain that will successfully prevent its transition to chronic pain. Such approaches should incorporate biological, psychological, and social aspects, and consider pragmatic aspects to dissemination and implementation.

Optimizing Approaches to Acute Postsurgical Acute Pain

Recognition has been growing that surgery can be a risk factor in the development of chronic pain.[36] For some surgical procedures, such as mastectomy and amputation, the incidence of chronic post-surgical pain can be as high as 50%.[99] Because of the large and growing number of surgical procedures performed each year in the United States (eg, an estimated 3.5 million total knee arthroplasty and total hip arthroplasty procedures will occur in 2030), there is potential for many individuals to develop chronic pain after acute postsurgical pain.[81] Currently, there is a dearth of literature regarding optimal strategies to manage acute postsurgical pain, particularly in light of risk factors including genetics, medical history, musculoskeletal health, and psychosocial well-being. An overview of mediators and moderators that may affect the effectiveness of approaches to managing acute postsurgical pain is provided in the Cross-Cutting Mediators/Moderators section.

Tertiary Pain Prevention

When chronic pain is present, it is necessary to shift the focus of prevention efforts from secondary to tertiary prevention, defined as reducing the frequency, severity, and effect of chronic pain by improving physical and emotional functioning.[62,111,124] Chronic pain conditions may not inevitably cause significant disability. Research into tertiary pain prevention should focus on: identifying risk factors for disabling chronic pain; developing interventions aimed at reducing the effect of chronic pain; optimizing available interventions; implementation of effective approaches in managing chronic pain; and high-priority subgroups.

Identification of Risk Factors for Disabling Chronic Pain

Although tertiary pain and disability prevention efforts should be addressed at everyone with chronic pain, it is particularly important to develop approaches aimed at the subset of individuals who will experience severe and disabling chronic pain that greatly limits their quality of life, ability to work, and engage in activities of daily living. To do so, it is necessary to develop screening tools intended for use among individuals who already have chronic pain (ie, are not designed to identify the risk of developing chronic pain) to identify those who are at greater risk of experiencing worsening and disabling chronic pain.

Effectiveness of Early Interventions for Tertiary Prevention

Although pain and disability prevention efforts are more likely to be effective during the acute and subacute phases, there may nevertheless be a "time window" in the early stage of chronic pain when it is still possible to reverse it, before neurological changes (eg, central sensitization) make this more difficult.[5,26,86] Research is needed to develop interventions aimed at individuals with recent-onset chronic pain conditions (eg, osteoarthritis), with the goal of maintaining or improving their quality of life and function, rather than attempting to "cure" chronic pain per se. Such interventions could potentially be cost-effective if they reduce exposure to expensive, invasive, harmful, or ineffective therapies for chronic pain (eg, spinal fusion for axial low back pain).[42] These interventions could be built around mitigating the influence of the risk factors identified in screening tools, similar to the STarT Back risk-based intervention.[63] More research is also needed to compare different strategies for selecting patients at higher risk of developing severe and disabling chronic pain.

Optimal Therapies for Tertiary Prevention

A large number of therapies are currently used for chronic pain patients including active approaches designed to improve function (eg, exercise therapy, psychological therapy, mind-body therapy, and interdisciplinary rehabilitation) and passive approaches that are mainly intended to improve symptoms (eg, medications, acupuncture, massage, manipulation, physical modalities). However, research is greatly needed to guide the optimal use of such active and passive therapies for specific types of chronic pain, many of which have a limited evidence base.[18,125] More study is also needed to identify subgroups of patients who may benefit more from active approaches, how those approaches should be delivered (eg, efficacy of individual components, effect of the order of treatments on efficacy), and how they can be tailored to individuals on the basis of specific risk factors present (eg, fear avoidance). Examples of novel research methods to evaluate these questions include Sequential, Multiple Assignment, Randomized Trial and Multiphase Optimization Strategy Trial study designs.[32,77]

Research to Evaluate Effects of Opioids in Terms of Impacting on Recovery

Although developed primarily for severe acute pain, opioids have become increasingly prescribed for chronic pain in the United States.[45] However, evidence indicates that opioids may have only modest or no effects on improving function for individuals with chronic pain recovery, and their use may in fact negatively affect functional recovery.[31] For example, studies of patients with

headaches indicate that opioids are not only not beneficial to reduce pain, but they can also result in analgesic-rebound headaches.[9,83] More research is needed to understand the effects of opioids on function and recovery from chronic pain, including studies that evaluate long-term outcomes related to disability and return to work after initiating opioid treatment. Research should compare the overall benefits of studies that compare the effects of opioids with nonopioid active therapies (eg, exercise therapies, work hardening), psychosocial therapies (eg, cognitive-behavioral therapy, biofeedback, and others), mind-body interventions (eg, yoga, mindfulness-based stress reduction), interdisciplinary approaches (eg, functional restoration), and nonopioid medications to inform their use in tertiary pain prevention strategies.[52]

Implementation Research

Research is also needed to develop more effective strategies to implement existing approaches with proven efficacy (eg, interdisciplinary rehabilitation) and overcome obstacles, such as lack of insurance coverage, high costs, and heterogeneity that have limited their use.[52] Pragmatic research is needed to understand how to offer and sustain interdisciplinary rehabilitation programs for tertiary pain prevention. For example, such programs could be offered in primary care settings, either by providing additional training to existing primary care providers, or integrating specialists in chronic pain or other HCPs (eg, psychologists, physical therapists, complementary and integrative medicine providers) into primary care clinics to improve access to care and treatments. Research is also needed to examine implementation strategies to incorporate these approaches into the workplace and home, understand how patient adherence affects the effectiveness of tertiary prevention interventions, and develop methods to encourage and maintain patient engagement. A better understanding of how provider and patient beliefs and behaviors can affect the long-term success of tertiary pain prevention approaches is also necessary.

High-Priority Populations

Research is also needed to examine the efficacy of existing approaches to tertiary pain prevention (eg, interdisciplinary rehabilitation) among vulnerable and high-priority populations that have seldom been studied in this field. These groups include children, adolescents, older adults, and pregnant women, as well as racial and ethnic minorities. The effectiveness of tertiary pain prevention interventions may differ in these groups from that in the "general" population, and it may be necessary to modify interventions to improve their effectiveness. Such modifications could also provide additional insight into improving tertiary pain prevention interventions and studies in the "general" population. Researchers involved in tertiary pain prevention should also consider whether their findings are applicable to all populations, and consider if statistically significant results are likely to affect clinically meaningful changes in vulnerable populations.

Transition From Acute Pain to Chronic Pain

In addition to investigations of screening tools and interventions to identify individuals with acute pain at greater risk of developing chronic pain, research is also needed about the basic epidemiology of this transition, with longitudinal studies that examine the different trajectories that may occur from the onset of acute pain to its becoming chronic (see the FPRS Transition WG for further discussion and recommendations on this topic). Currently, we do not have sufficient knowledge about the mechanisms through which acute pain becomes chronic pain, including whether this transformation occurs incrementally or suddenly. It has been assumed—but not empirically supported—that pain undergoes a linear and permanent transition from acute to subacute and then chronic pain at specified time intervals.[51,54,126] This assumption is incorrect, as studies have also demonstrated independent trajectories of recovery.

Trajectories of Recovery

Studies on this transition in low back pain has led researchers to suggest that it should be viewed as a persistent or recurrent problem rather than a self-limiting condition.[5,86,126] This is on the basis of studies reporting that, although the initial episode of acute low back pain may be short-lived, it often recurs and fluctuates in severity over time rather than disappearing completely. At least 5 subgroups have been identified in the trajectory of function related to low back pain over a 1-year period, including: 1) stable low disability, 2) stable low-moderate disability, 3) stable moderate-high disability, 4) stable high disability, and 5) recovery.[41] The same study identified 6 subgroups for trajectories of pain severity related to low back pain, including 4 with different starting points but minimal improvement, and 2 with improvements (moderate pain recovery and severe pain recovery). The notion that "flare-ups," recurring episodes, residual pain, and reduced function may be the norm after an initial episode of acute low back pain contrasts sharply with beliefs that acute low back pain has a favorable prognosis and resolves spontaneously.[69]

Trajectories have also been identified in the recovery of whiplash-associated disorders (WADs) by measuring outcomes repeatedly over time and creating clusters of individuals with similar changes in outcomes, which also provided an opportunity to explore nonlinear changes.[25] For example, one study examined recovery trajectories for patients with WAD who were recruited within 1 month of their injury and followed for 12 months.[117] Three distinct trajectories of recovery were identified for changes on the Neck Disability Index: 1) mild (ie, mild pain/disability for the entire 12 months), 2) moderate (ie, pain/disability was initially moderate but improved to mild), and 3) severe (ie, pain/disability was initially severe and remained moderate to severe). Trajectories of recovery were also observed among individuals with WADs who filed a compensation claim and were followed for 24 months.[25] Overall, approximately one-half of the population was likely to fully recover, but half was likely to report some degree of ongoing neck-related disability

or psychosocial dysfunction. These changes were not linear, with some subgroups improving materially in the first 2 to 3 months but plateauing after 6 months; the period of improvement is probably an important timeframe period for interventions aimed at preventing further pain and related disability.[116]

Methods to Examine the Transition From Acute to Chronic Pain

Longitudinal examinations of the transition from acute to chronic pain can be undertaken with inception cohorts, using tools such as daily electronic diaries accessed on smart phones to measure pain severity, function, and other relevant outcomes.[70] When common trajectories of recovery are delineated for specific pain conditions, they can provide guidance to researchers examining biological processes (eg, biomarkers) that may explain these changes. This information may also affect the development and implementation of screening tools and personalized interventions intended to alter these trajectories by focusing on potential "windows of opportunity" during which they would have the most impact.

Cross-Cutting Mediators/Moderators

Additional areas for research were also identified across overlapping topics related to the prevention of acute and chronic pain, including: 1) mechanisms underlying responses to various interventions, 2) optimizing multimodal interventions, 3) adherence to interventions, 4) mediators of outcomes, 5) matching interventions to responders, and 6) improving efficiency of delivering interventions. Recommendations in each area are briefly summarized in the following sections.

Mechanisms Underlying Response to Various Interventions

There is considerable variation in individual responses to different interventions for acute and chronic pain, which may be related to genetic variations in the perceptions of, and responses to, noxious stimulation (eg, sensory sensitivity, initiation, and persistence of pain).[43] For example, researchers have reported that the effects of catastrophizing may be moderated by a genetic diplotype (eg, catechol-O-methyltransferase).[55] Additional research could potentially identify individuals who are predisposed to experiencing significant pain severity after trauma (eg, surgery, motor vehicle collision) to teach adaptive self-management skills and prevent this.

Additional research is also required to explore the use of brain imaging and biomarkers in our understanding of pain, because multiple, integrated cortical systems are involved in experiencing pain, including the prefrontal cortex (ie, processing the meaning of pain), the anterior cingulate cortex (ie, processing the emotional or affective response to pain), and the insula (ie, processing information related to a physical condition and associated motivation).[2,72,73]

Functional magnetic resonance imaging could be used to identify regions of the brain associated with processing sensory, emotional, and cognitive information associated with pain and behavioral responses (eg, catastrophizing is associated with the cerebellum, prefrontal cortex, claustrum, parietal cortex, and dorsal anterior cingulate gyrus).[3,57,80,109] Such information could help explain how interventions that alter pain-related thoughts (eg, cognitive-behavioral therapy could be beneficial by altering activity and processes in the prefrontal cortex, whereas interventions that alter physical comfort and psychological calm (eg, relaxation training, biofeedback, hypnosis) could alter activity and processing in the sensory cortex and limbic system.[7,21,46,49,73] It has also been reported that pain catastrophizing is correlated with pain sensitivity, suggesting that catastrophizing may attenuate the descending inhibitory system.[130] Other studies have reported an association between diminished prefrontal cortical modulation and catastrophizing under painful stimulation,[109] and that catastrophizing may be related to activation of cortical regions involved in attentional, anticipatory, and emotional responses to pain, suggesting that increased attention and anticipation of pain may worsen it.[57] If links between psychosocial therapies for pain prevention and specific changes in pain-related brain activity or structures are clarified, it might be possible to develop more effective approaches (eg, combining functional magnetic resonance imaging biofeedback with cognitive-behavioral therapy) to target the regions involved.

Optimizing Multimodal Interventions

The complexity of chronic pain and the modest benefits of many available interventions suggest that monotherapies are unlikely to be effective, and should be combined to benefit from additive, or even synergistic, effects on outcomes, including safety and efficacy.[123] Moreover, it may be possible to create customized multimodal approaches on the basis of individual needs.[11,17,37,50,64,76,102,103,114] For example, practice-based evidence designs have been used in observational studies to discover combinations of therapies associated with better outcomes.[65] However, additional research is needed to study multimodal interventions, including: 1) the choice of which combination therapies to study, 2) determining an appropriate sample size, 3) the logistics of providing standardized approaches to multimodal therapies, 4) the ability to blind outcome assessors, and 5) attribution of adverse events to specific components of multimodal interventions. Although promising, the complexity of multimodal interventions to prevent pain requires considerable forethought, pilot studies, and organization of research efforts.

Adherence to Interventions

Although many interventions used in acute and chronic pain are initially beneficial, their benefits are usually not sustained for various reasons, including nonadherence to long-term treatment recommendations that require

ongoing self-management (eg, medication, smoking cessation, weight control).[16,19,106] Previous research has identified risk factors for nonadherence (eg, individual traits, social support, provider interactions, treatment complexity, side effects), but these findings have not led to the development of interventions to mitigate these factors.[61,74,97] More research is needed to identify and address key factors in nonadherence to interventions aimed at pain prevention, including possible interactions among these factors.

Mediators of Outcomes

Heterogeneity in treatment outcomes should be explored by examining treatment mediators (ie, factors changed as a result of the treatment) and identifying how changes in those factors may have affected the outcome of interest on the basis of temporality.[75,79] For example, if a treatment reduces fear-avoidance beliefs and leads to improved function, it is also possible that improved function occurred first, reducing fear-avoidance beliefs. Without serial measurement (ie, minimum of 3 time points) of the proposed mediator (ie, fear avoidance beliefs) as well as outcome (ie, function), it is not possible to determine how this change occurred.[128] Use of mediation analysis (eg, latent growth modeling) enables a greater examination of these variables across time, within as well as between participants exposed to interventions.[24] Such research could help identify the mechanisms of different interventions for pain prevention and maximize their effectiveness, potentially using neuroimaging techniques.[7,21,46,49,71,95,132]

Matching Interventions to Responders

Additional research is also needed to better understand and predict individual responses to specific interventions, rather than focusing solely on group-mean effects that imply a homogeneous response for all individuals in a group, rather than subsets of hyper-, hypo-, and nonresponders. Matching patients to specific interventions on the basis of known predictors could greatly improve treatment efficiency, which could potentially be achieved by extensive data collection about each patient's illness (eg, Comprehensive Severity Index and other characteristics that could affect outcomes in subgroup analyses).[122] When predictors are proposed, and individualized treatment recommendations are made on the basis of predicted responses, studies could assess whether such customized treatments are effective, or can further be improved by examining nonresponders. Such research would shift the focus away from asking if a specific treatment is effective for all patients and ask, instead, which treatment is effective for a specific patient.

Improving Efficiency of Delivering Interventions

Some of the successful interventions available to manage chronic pain (eg, interdisciplinary rehabilitation) require substantial resources, including appropriately-trained behavioral therapists and other HCPs who may not be available outside large urban areas and academic centers. Research is needed to explore delivering effective behavioral interventions for pain using non-behavioral specialists, including lay providers,[87,88] nurses, and physical therapists.[10,15,20,66] Novel methods of delivering preventive pain care should also be explored, including computerized games to promote exercises,[8,39,59,96,112,121] internet-based interventions to promote behavioral change,[91,105,107] smartphone applications, and social media to enhance and monitor care,[82,84,85,110] and machine learning to customize interventions.[14,23,38,44,107,118] Additional research is also necessary to determine how to generate, analyze, and interpret findings from large data sets (ie, "big data") in real-time to monitor responses to care. These strategies could address barriers to accessing care, reduce costs, improve efficiency of delivery, and improve outcomes by facilitating long-term adherence.

Conclusions

The FPRS seeks to identify critical knowledge gaps related to: the prevention of acute and chronic pain, acute pain and acute pain management, transition from acute to chronic pain, chronic pain and chronic pain management, disparities in pain and pain care, and cross-cutting issues, for federally-sponsored research programs to address them and, ultimately, reduce the effect of pain in the United States. The WG on the Prevention of Acute and Chronic Pain recommended that future research in this area should focus on fillings gaps related to the epidemiology of acute pain from health care procedures, epidemiology of acute pain from work-related injuries, safety and effectiveness of management of pain associated with health care procedures, optimizing approaches to acute postsurgical pain, and safety and effectiveness of early interventions for the tertiary prevention of pain. Members of this WG believe that addressing these gaps could contribute substantially to the understanding, development, and implementation of efforts aimed at preventing the onset, duration, and severity of pain. The rationale for each of these recommendation was provided in this report to encourage and facilitate future research on these topics. Researchers, HCPs, policy makers, patients, and other interested stakeholders should consider implementing these recommendations when interacting with federal agencies involved in supporting pain research in the United States.

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