Transition to chronic pain: opportunities for novel therapeutics

Theodore J. Price[1], Allan I. Basbaum[2], Jacqueline Bresnahan[2], Jan F. Chambers[3], Yves De Koninck[4], Robert R. Edwards[5], Ru-Rong Ji[6], Joel Katz[7], Annemieke Kavelaars[8], Jon D. Levine[2], Linda Porter[9], Neil Schechter[5], Kathleen A. Sluka[10], Gregory W. Terman[11], Tor D. Wager[12], Tony L. Yaksh[13] and Robert H. Dworkin[14]*

Although chronic pain is one of the most important medical problems facing society, there has been very limited progress in the development of novel therapies for this condition. Here, we discuss high-impact research priorities to reduce the number of people transitioning from acute to chronic intractable pain.

[1]*The University of Texas at Dallas, Richardson, TX, USA.*

[2]*University of California, San Francisco, San Francisco, CA, USA.*

[3]*National Fibromyalgia and Chronic Pain Association, Logan, UT, USA.*

[4]*Laval University & CERVO Brain Research Centre, Québec, QC, Canada.*

[5]*Harvard University, Boston, MA, USA.*

[6]*Duke University, Durham, NC, USA.*

[7]*York University, Toronto, ON, Canada.*

[8]*University of Texas MD Anderson Cancer Center, Houston, TX, USA.*

[9]*National Institutes of Health, Bethesda, MD, USA.*

[10]*University of Iowa, Iowa City, IA, USA.*

[11]*University of Washington, Seattle, WA, USA.*

[12]*University of Colorado, Boulder, CO, USA.*

[13]*University of California, San Diego, San Diego, CA, USA.*

[14]*University of Rochester, Rochester, NY, USA.*

*e-mail: Theodore.price@utdallas.edu

https://doi.org/10.1038/s41583-018-0012-5

Despite widespread recognition of the importance of developing better interventions for chronic pain, little progress has been made. To address this unmet public-health need, the Interagency Pain Research Coordinating Committee of the US National Institutes of Health (NIH) convened working groups to develop a research agenda for the Federal Pain Research Strategy. This article summarizes some of the recommendations that have been included in that report. Our working group focused on the transition from acute to chronic pain.

We identified several overarching conceptual issues that need to be addressed to advance our understanding of chronic pain. First, various clinical risk factors have been identified that predispose individuals to chronic pain (for example, extensive nerve damage during surgery). The results of preclinical animal studies have demonstrated a key role for neuronal plasticity and nervous system interactions with the immune system in chronic pain states[1]. Brain imaging studies in patients have consistently revealed changes in brain function and anatomy as pain becomes chronic[2]. A comprehensive picture of how these findings may come together to promote the acute to chronic pain transition represents a major gap in our knowledge (Supplementary Figure 1).

Second, when does the transition to a chronic pain state occur? It is widely assumed that the transition happens some period of time after the onset of acute pain, but it is also possible that acute and chronic pain mechanisms commence simultaneously in people whose pain persists.

Third, many different mechanisms can promote the development of chronic pain (reviewed in REF.[3]) but these disparate mechanisms can result in strikingly similar phenotypes. Importantly, as most human studies only assess phenotypes, we often have little knowledge of the underlying molecular mechanisms in patient populations and few tools available to elucidate those mechanisms. Therefore, there is a deepening knowledge gap between non-human animal and clinical studies. This gap can be addressed by developing technology to define physiological and molecular mechanisms in humans and expanding the range of phenotypic pain behaviours assessed in animal studies.

Fourth, it is unclear whether the path to treatment of chronic pain states necessarily involves targeting of the mechanisms that caused the pain to become chronic or if there are separate endogenous pain-resolution mechanisms that can reverse the course of chronic pain. On the basis of these overarching issues, we identified three major research priorities.

Transition mechanisms and therapies

It is now clear that the transition to chronic pain fundamentally changes neuronal phenotypes and/or circuits rendering acute pain medicines less effective. New pain treatments are needed that will benefit patients with chronic pain. These could include novel, non-opioid analgesics, more efficacious non-pharmacological treatment approaches and novel opioid analgesics with decreased abuse liability[4]. Another important development would be the discovery of the first disease-modifying treatments for chronic pain.

To realize these more effective pain treatments, we identified two priorities. First, a focus should be placed on drug and other forms of therapeutic discovery (for example, non-pharmacological modalities) to develop treatments that simultaneously block acute pain and the mechanisms that promote development of chronic pain. Second, therapeutics should be created that mimic or target endogenous pain-resolution mechanisms to reduce and potentially permanently reverse chronic pain (Supplementary Figure 2). Basic discovery research in these areas should be encouraged in the academic community and via academic–industry partnerships.

To enable the discovery of new therapeutics, novel tools and technologies have to be developed to bridge

gaps between advances in preclinical research and our understanding of chronic pain in humans. These include advances in next-generation sequencing and/or imaging to characterize the mechanisms and risk factors that drive pain-related plasticity in patients. As human tissue availability continues to expand, avenues of research leveraging these resources with new technologies in cell biology should be pursued to rigorously evaluate plasticity and resolution mechanisms that were discovered in animal models in humans. Moreover, researchers should take advantage of human stem cells to hone in on new pain mechanisms and, potentially, to better treat chronic pain. For instance, as has been shown in preclinical models, stem cells may be utilized to enhance or replace elements of the 'pain circuitry' that have gone awry in chronic pain[5].

Researchers should also utilize and/or engineer new technologies for the assessment of brain network connectivity changes in preclinical models that may add considerable molecular insight to human imaging work. Parallel advances in this area may enable discovery of therapeutic strategies that will target the myriad of brain abnormalities that emerge with chronic pain.

Finally, findings in animal models suggest that certain acute pain therapeutics can enhance the transition to chronic pain. This paradox should be investigated prospectively. Conceivably, some strategies for relieving acute pain may impair resolution mechanisms, as has been suggested for opioids in animal models.

Identifying group differences

Unfortunately, very little attention has been paid, in the US and elsewhere, to studying chronic pain in some populations. Research aimed at the transition to chronic pain in populations that have traditionally been ignored or excluded from study could have a large impact on the prevalence of chronic pain. Although there have been recent advances, it is still largely unknown how early-life experience influences chronic pain. Do pain mechanisms differ at birth, in childhood and/or during adolescence from those later in life? Recent research suggests that there are critical periods in which individuals are relatively protected from the development of injury-induced or disease-induced chronic pain. For instance, postherpetic neuralgia, which often follows an episode of shingles in older adults, rarely occurs in children. Research targeting the mechanisms that underlie age-dependent differences has great potential for the discovery of novel pain-resolution mechanisms and therapeutic strategies.

Chronic pain mechanisms in women have almost entirely been ignored, a fact that is highlighted by a recent, much needed change in NIH policy. Chronic pain is more prevalent in women than men and preclinical studies increasingly demonstrate mechanistic differences in molecular pathways that promote chronic pain between the sexes. It may, in fact, be a mistake to expect therapeutics that are effective in women to be equally effective in men and vice versa. It is also clear that changes in hormone and neuroendocrine levels occur across the lifespan, in a sex-dependent fashion, and are likely important contributors to the transition from acute to chronic pain. These mechanisms are poorly understood and not widely studied. Expanding research effort in this area could advance the objective of developing personalized pain medicine.

Mechanism-targeted clinical trials

Cross-sectional studies document the incidence of chronic pain, but to determine causes for the transition to chronic pain, prospective longitudinal studies must be conducted. A goal should be to study clinical populations in which protective factors can be identified and integrated with known risk factors, such as more severe acute pain. These prospective studies should also capitalize on new technologies and new basic science knowledge (for example, sequencing of defined cell populations) to identify mechanisms of transition to chronic pain prospectively in patients. Such studies may identify interventions that can then be examined in clinical trials.

Mechanistic clinical trials that target risk and/or endogenous pain-resolution factors are the most informative approach to studying putative preventive interventions[6]. For example, does pharmacological or non-pharmacological attenuation of high levels of acute pain or central sensitization, or augmentation of descending inhibition, reduce the risk that patients will develop chronic pain? Outcomes that are meaningful to patients, such as functional recovery, should be assessed in such mechanistic trials; simply measuring pain is not adequate. The development of biomarkers of chronic pain is also essential.

Conclusions

As inadequate treatment options for chronic pain place an immense burden on patients, families, health-care systems and our society, and are probably important contributors to the overuse of prescription opioids, scientific progress in the areas highlighted above is essential. Initiatives to identify valid biomarkers, to investigate the acute to chronic pain transition in large patient cohorts and to establish pain clinical trial networks are being developed. These efforts and the rest of the research agenda outlined here will hopefully advance the field and create new opportunities for near-term and long-term breakthroughs that will decrease the incidence and impact of chronic pain.

1. Ji, R. R., Chamessian, A. & Zhang, Y. Q. *Science* **354**, 572–577 (2016).
2. Apkarian, A. V., Baliki, M. N. & Farmer, M. A. *Curr. Opin. Neurol.* **26**, 360–367 (2013).
3. Denk, F., McMahon, S. B. & Tracey, I. *Nat. Neurosci.* **17**, 192–200 (2014).
4. Skolnick, P. & Volkow, N. D. *Neuron* **92**, 294–297 (2016).
5. Braz, J. M. et al. *Neuron* **74**, 663–675 (2012).
6. Gewandter, J. S. et al. *Pain* **156**, 1184–1197 (2015).

Acknowledgements
We thank the Interagency Pain Research Coordinating Committee of the US National Institutes of Health, who facilitated and provided financial support for meetings of the working group.

Competing interests
The authors declare no competing interests.

Supplementary information
Supplementary information is available for this paper at https://doi.org/10.1038/s41583-018-0012-5.

RELATED LINKS
Federal Pain Research Strategy: https://iprcc.nih.gov/sites/default/files/iprcc/FPRS_Research_Recommendations_Final_508C.pdf
NIH policy: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html