Pots of gold and winning lottery tickets

the never-ending search for predictors of chronic pain

Cohen, Steven P.; Ciampi de Andrade, Daniel

Published in:
Pain

DOI (link to publication from Publisher):
10.1097/j.pain.0000000000002685

Publication date:
2023

Document Version
Accepted author manuscript, peer reviewed version

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000002685

Pots of gold and winning lottery tickets: the never-ending search for predictors of chronic pain

Steven P. Cohen[a], Daniel Ciampi de Andrade[b]

[a]Depts. of Anesthesiology & Critical Care Medicine, Neurology, Physical Medicine & Rehabilitation and Psychiatry & Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, and Walter Reed National Military Medical Center, Uniformed Services University of the Health Sciences, Bethesda, MD;

[b]Center for Neuroplasticity and Pain, Department of Health Sciences and Technology, Faculty of Medicine, Aalborg University, DK-9220, Aalborg, Denmark.

Corresponding author: Steven P. Cohen, Department of Anesthesiology and Critical Care Medicine, Division of Pain Medicine, Johns Hopkins University, 600 N. Wolfe St, Phipps 460, Baltimore, MD 21287. Telephone: (410) 955-1822. Fax: (410) 614-2019. E-mail: scohen40@jhmi.edu

The authors report no conflicts of interest.

Keywords: back pain; chronification; neuroimaging; cortical excitability

Everyone gets injured. One might view getting hurt as an integral part of life, similar to eating and working. In this context, acute pain serves as a teleological warning system, alerting an

organism to actual or impending tissue damage. In contrast, chronic pain is nearly always pathological, as it no longer serves an evolutionarily advantageous purpose (4) and its intensity does not always correlate with tissue injury. Since most people who develop acute pain heal with minimal sequelae, performing expensive diagnostic tests with low specificity for all people is neither practical nor cost-effective. Hence, identifying those at risk to transition from acute to chronic pain has become one of the top priorities for pain researchers, akin to finding the proverbial pot of gold at the end of the rainbow, picking the winning lottery ticket, or even the Holy Grail.

The premise of weaving together risk factors to build prognostic models assumes that identification of patients at high risk of developing chronic pain will allow for targeted interventions to avoid chronification. There is optimism embedded in this clinically coherent rationale, but such an approach has yet to prove practical. It is unknown whether markers of worse prognosis reflect conditions that are modifiable, or rather portend an inexorable path towards pain persistence unamenable to interventions. In other words, is this like telling a patient we found cancer but there's nothing we can do about it, or telling them we detected an early-stage tumor but might be able to alter the natural trajectory? As acknowledged by the authors, some of these markers may merely be epiphenomena that possess no causal relationship with pain persistence.

Since low back pain (LBP) is one of the leading causes of disability worldwide, it is a prime candidate for research that aims to determine risk factors for chronification (6). In the UPWaRD trial, Jenkins et al. led researchers in a cohort study whose aim was to identify factors associated with the pain at 6 months in 120 patients with new onset or acute recurrent axial LBP, focusing on cortical sensorimotor excitability. Other factors examined included measures of

disease burden (e.g., pain and disability scores), psychosocial variables, brain-derived neurotrophic factor genotyping and serum levels, general health, and health utilization. Most of what they found was not surprising: individuals with psychopathology, who catastrophize, who had greater baseline healthcare utilization and disease burden, with certain genotypes, and who reported greater pain interference had poorer outcomes. However, they demonstrated for the first time that adding cortical excitability to classic risk factors led to an increase in model predictability. It was reported that abnormal motor evoked potential (MEP) amplitudes are associated with acute and persistent experimental pain, and in some instances chronic pain (10,11). In their study (8), the authors showed that low sensory cortex excitability and low MEP volume of paraspinous muscles obtained by transcranial magnetic stimulation were positively associated with pain intensity at 6 months. These variables increased the strength of an otherwise inclusive model by 15%, which represents a modest but clinically meaningful refinement of an otherwise robust multimodal prediction model.

One of the most appealing aspects of 'PAIN' and its sponsor, the International Association for the Study of Pain, is that they are multidisciplinary and international. Research papers with limited geographical appeal, and those relevant to only a small segment of the pain community are less likely to be published in PAIN. In this regard, Jenkins et al. (8) should be applauded. They chose a condition to study that has reached 'pandemic' proportions and selected a wide range of variables that include psychological, social, neuroscience, and genetic candidates. Yet, from the perspective of specialists, there are still several shortcomings. Only 3 of 498 screened patients were excluded for radicular pain, which is an exponentially lower percentage than that observed in larger, similar cohort studies performed in acute LBP patients, and the proportion of individuals with chronic LBP deemed to have a neuropathic component

(5,7). Moreover, it is likely that many of these people, particularly those with recurrent LBP, have what is now termed 'nociplastic' pain, or non-specific LBP, which may have a different prognosis than mechanical LBP (1,4). This suggests the possibility of a more heterogeneous cohort than the authors anticipated, and may undermine generalizability. Second, although the authors considered numerous variables- perhaps too many to support a stable regression model for the 96 patients who completed 6-month follow-up- they did not consider historical or physical exam findings, which despite the plethora of impressive tests available to specialists, are still a mainstay of any LBP evaluation. For example, one might expect back pain from muscle spasm, which can be identified by physical or ultrasound exam, to completely heal in a few weeks, while sacroiliitis, which can be reliably identified by a battery of historical and physical exam signs, may be more likely to persist (9,12). Recent studies have also shown that non-organic (Waddell) signs, which require minimal effort to ascertain, may predict back pain persistence and treatment outcome (3,13). Last, adding simple information such as patients' expectations towards recovery and personal beliefs regarding LBP might further improve the model.

It should be pointed out that the main study outcome was pain intensity at 6-months, with the presence of pain being a secondary outcome. Therefore, chronic pain (pain persisting for > 3 months) was not actually assessed, meaning that patients presenting with a second episode of LBP right before the 6-month assessment were analyzed in the same manner as those developing *de novo* chronic LBP after the acute episode; this is relevant since 23% of analyzed patients had recurrent, rather than new-onset LBP. It also remains to be determined whether pain intensity at 6 months translates into clinically meaningful outcome from the patients´ perspective in terms of

quality of life. From a 10,000-foot view, it would be interesting to see whether these findings generalize to the general pain population at-large.

So how can these results be used clinically, or as a springboard for further research? At this point in time, there is unknown value in routinely genotyping patients, obtaining non-routine labs, or performing neurophysiological testing on all patients who develop acute LBP, which may approach 100% prevalence in some physically-active populations such as active-duty military and is likely to resolve in most individuals, especially those who don't seek medical care (2). Yet, the push for a more personalized medicine approach within a biopsychosocial framework may someday support pursuing more expensive and resource-intensive tests in individuals deemed at high-risk in an effort to prevent the even more expensive and resource-intensive treatment of chronic LBP. Future studies might seek to refine candidates for functional imaging and genotyping, determine whether interventions can actually prevent chronic LBP, and evaluate cost-effectiveness.

References

1. Clauw DJ, Essex MN, Pitman V, Jones KD. Reframing chronic pain as a disease, not a symptom: rationale and implications for pain management. Postgrad Med 2019; 131: 185–98.
2. Carragee EJ, Cohen SP. Lifetime asymptomatic for back pain: The validity of self-reported measures in soldiers. Spine 2009; 34: 978-83.
3. Cohen SP, Doshi TL, Kurihara C, Dolomisiewicz E, Liu R, Dawson TC, et al. Waddell (nonorganic) signs and their association with interventional treatment outcomes for low back pain. Anesth Analg 2021; 132: 639-51.

4. Cohen SP, Vase L, Hooten WM. Chronic Pain: An update on burden, best practices and recent advances. Lancet 2021; 397: 2082-97.
5. Fishbain DA, Cole B, Lewis JE, Gao J. What is the evidence that neuropathic pain is present in chronic low back pain and soft tissue syndromes? An evidence-based structured review. Pain Med 2014; 15: 4-15.
6. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396: 1204-22.
7. Hüllemann P, Keller T, Kabelitz M, Gierthmühlen J, Freynhagen R, Tölle T, Forstenpointner J, Baron R. Clinical Manifestation of Acute, Subacute, and Chronic Low Back Pain in Different Age Groups: Low Back Pain in 35,446 Patients. Pain Pract 2018; 18: 1011-23.
8. Jenkins LC, Chang WJ, Buscemi V, Liston M, Humberg P, Nicholas M, et al. Cortical function and sensorimotor plasticity are prognostic factors associated with future low back pain after an acute episode: the UPWaRD prospective cohort study. PAIN 2022 (in press).
9. Malanga GA, Cruz Colon EJ. Myofascial low back pain: a review. Phys Med Rehabil Clin N Am. 2010; 21: 711-24.
10. Schabrun SM, Christensen SW, Mrachacz-Kersting N, Graven-Nielsen T. Motor Cortex Reorganization and Impaired Function in the Transition to Sustained Muscle Pain. Cereb Cortex 2016; 26: 1878-90.

11. Thapa T, Graven-Nielsen T, Chipchase LS, Schabrun SM. Disruption of cortical synaptic homeostasis in individuals with chronic low back pain. Clin Neurophysiol 2018; 129: 1090-6.
12. Thawrani DP, Agabegi SS, Asghar F. Diagnosing sacroiliac joint pain. J Am Acad Orthop Surg 2019; 27: 85-93.
13. Werneke M, Harris D, Lichter R. Clinical effectiveness of behavioral signs for screening chronic low back pain patients in a work oriented physical rehabilitation program. Spine (Phila PA 1976) 1993; 18: 2412-8.