

Clinical and neuroscience evidence supports the critical importance of patient expectations and agency in opioid tapering

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In 2014, 11 million Americans were taking daily prescription opioids.²⁹ However, because of widespread opioid addiction and overdose deaths, there is continuing controversy on the optimal use of opioid analgesics for chronic pain. In response to the tragic rise in opioid overdose deaths, the U.S. Centers for Disease Control and Prevention (CDC) issued the 2016 *Guideline for Prescribing Opioids for Chronic Pain*.¹⁴ Subsequently, opioid prescriptions dropped by as much as 57% per year (2016-2019).⁷ By 2017, about 23% of patients taking prescribed opioids were being tapered or discontinued.¹⁶ Although the most common rationales for discontinuing or dose reduction were that opioids were ineffective or had unacceptable side effects, the CDC cited 2 additional reasons: first, weak evidence for opioid efficacy beyond 3 months and, second, preclinical and human studies indicating that opioid exposure could result in hyperalgesia.⁵ Additional reasons for tapering include the risk of use disorder, overdose, and diversion.

Although opioid tapering was intended to improve patient safety and health by avoiding opioid use disorder, overdose and diversion, and to mitigate opioid-induced worsening of pain, outcome studies indicate that tapering introduces new risks and patient harms. Indeed, reduction or discontinuation of prescribed opioids can actually increase risks for overdose,^{1,22,30} overdose deaths,²⁵ all-cause mortality,^{23,25} and suicide.³² In addition, some studies have documented increased pain, fear of pain,³⁰ and mental health crises including suicidal ideation.^{1,12} In 2019, the American Medical Association,⁴ the CDC,¹³ the U.S. Food and Drug Administration,¹⁸ and others⁹ issued warnings about tapering practices that exposed patients to these iatrogenic risks.

Most taper studies report that opioid dose can be reduced and, in some cases, discontinued without a worsening of pain.²⁰ However, these studies were unblinded, nonrandomized, and had no

nontapered control group. Most tapering studies have not differentiated voluntary vs involuntary taper methods, although limited research comparing the 2 methods has suggested no group difference for pain intensity outcomes after taper.^{20,28} Although seemingly promising, the authors of one of these reports²⁰ cautioned against an interpretation that involuntary tapering is harmless; they noted that their outcome assessment was limited and “did not evaluate potential harms of involuntary tapering such as emotional distress, disruption of the patient-clinician relationship... and rare but serious harms such as hospitalization and suicide” (severe withdrawal, overdose, and other mortality were also not quantified).

Indeed, generalizability of the broader taper literature is limited by retrospective designs, exclusion of patients who have died during the study period or left care, and use of clinical data sets that do not capture individual patient-reported outcomes.³³ Importantly, they do not identify conditions with enhanced patient risk.²⁸ In view of significant variability in benefits and harms of taper, in its 2019 prescription opioid tapering guidance, the U.S. Department of Health and Human Services called for an individualized, patient-centered approach that accounts for potential opioid analgesic benefits and concluded that consensual tapering is ideal.²⁴

Building on this foundation, we argue that the success of an opioid taper can be improved using both neuroscience-based concepts and clinical data to understand individual patient variability for opioid analgesic treatment response. We specifically describe how factors such as expectation and agency dynamically contribute to patient outcomes and offer recommendations for successful opioid tapering in patients with chronic pain.

Pain is a predictive cue that signals threat of bodily harm. At any given level of stimulus intensity, a noxious stimulus that is rising is felt as more painful, whereas one that is falling is felt as less painful.^{2,35} Furthermore, through learning, neutral sensory cues become either pain (eg, nocebo) or relief predictive (eg, placebo).¹⁷ Human functional imaging studies confirm the idea that pain and relief predictive cues activate specific top-down pain modulatory circuits in the central nervous system including cortical links to spinal pain transmission neurons by striatal, mesencephalic, and pontomedullary relays to the spinal cord dorsal horn.^{15,35} These expectation activated descending circuits exert bidirectional control of pain by parallel descending pain modulating neurons, either suppression or facilitation.¹⁷

Patient expectations also robustly influence analgesic drug efficacy.^{6,8} One controlled study manipulated subject expectations to illustrate their impact on opioid analgesia.⁶ Healthy volunteers received experimental heat pain and intravenous administration of the opioid remifentanyl⁶ under 3 conditions in which they were told they were receiving: (1) a powerful painkiller, (2) saline, or (3) a pharmacological agent that would amplify their pain (nocebo). When subjects believed that they were receiving a powerful pain reliever

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(condition 1), the analgesic benefit of remifentanyl was doubled relative to when they believed they were receiving saline (condition 2). In addition, when subjects believed they were receiving a treatment that would amplify their pain (condition 3; placebo), the analgesic benefit of remifentanyl was abolished. Concurrent functional neuroimaging correlated with the subject report for increased pain for condition 3 and confirmed enhanced activity in brain areas typically activated by noxious stimuli.

Other research illustrates how patient expectations modulate opioid analgesia.³⁴ For example, when hidden and open administration of any analgesic drug are compared, pain relief is consistently and significantly greater when the drug is given openly.⁸ Previous experience with an effective drug enhances the effect of subsequent administration of a similar appearing placebo or active drug. Thus, the direct pharmacological effect of opioids on the central nervous system interacts robustly with patient expectations. If patient expectations are not managed explicitly, the analgesic effect of opioids could be reduced at the most precarious time: precisely when opioid doses are being reduced. In this situation, the likelihood that opioid taper will worsen pain is greatly increased.

Patients' sense of agency is also relevant. Studies of experimental pain in healthy volunteers consistently show that the lack of controllability enhances the perceived intensity of acute noxious stimuli.³¹ Similarly, clinical data suggest improved patient outcomes with increased controllability. A meta-analysis of postsurgical pain management revealed that the use of postsurgical patient-controlled analgesia yields significantly improved patient satisfaction ratings, small decreases in pain intensity, but only very small increases in opioid use (7 mg over 24 hours; 95% confidence interval = 1-13 mg).²⁷ Consequently, for patients with chronic pain, an expectation of increased pain and a lack of perceived control in the taper process may interact to increase pain intensity, reduce patient compliance, and thereby undermine the clinical effectiveness of an opioid taper.

As such, patient support for opioid dose reduction is critical. Randomized studies show that the multiweek support group and behavioral medicine sessions improve outcomes for opioid tapering,³² as well as for opioid reduction outside of a formal taper program.²¹

We caution against current policies and clinical practices, such as those documented in various U.S. state policies,¹⁹ that overlook the relevant clinical and neurobiological research. Mandates or guidelines are problematic if they fail to account for individual variability in drug metabolism and efficacy, relevant comorbidities, and overlook the importance of patient agency and expectations. Instead of feeling cared for, patients may feel trapped by rigid rules and ineffective pain control. Such circumstances may increase expectation for increased pain, activate top-down pain facilitating circuits, and lead to a poor taper response.

A small study (N = 68) of voluntary patient-centered opioid tapering in community outpatients with chronic pain offers relevant data and insights that extend beyond taper support and coping skills and directly pertain to the patient's sense of control over the taper process.¹¹ Potential placebo responses were mitigated by increasing patient choice and control. Patients were told the goal was to help them achieve their "lowest comfortable dose" over 4 months. Patients could (1) determine the taper pace, (2) pause their taper, (3) stop their taper and drop out of the study, and (4) increase their opioid dose if their result was poor. On average, there was a 50% reduction in opioid doses without increased pain. A follow-up study on a subset of patients found that their dose reductions and pain stability were maintained 2 to 3 years later.³⁶ These findings suggest that this individualized consensual approach promotes successful opioid dose reduction.

Two further issues bear consideration. First, in the original study, patients with greater levels of depressive symptoms were

more likely to drop out (N = 17), suggesting a need for additional support in this subpopulation. Second, and importantly, a subgroup of patients (18%) either had increased pain with taper or required an increased opioid dose. There are several possibilities that explain why people may not improve or worsen during a taper: (1) patients may be benefitting from long-term opioids and require the higher dose to achieve adequate analgesia, (2) there may be undiagnosed comorbidities (eg, anxiety or depression), and (3) the opioid effect may be unrelated to pain relief. Importantly, for patients taking opioids as prescribed, difficulty with tapering alone is insufficient evidence for a DSM-5³ opioid use disorder diagnosis.

We believe that endorsing patient control and agency during opioid taper is critical for optimal patient outcomes.²⁶ Currently, this individualized consensual approach is being extended to a large 4-state trial.¹⁰ To encourage patient retention and improvement, weekly surveys are used to rapidly identify and address patient discomfort and distress, including pausing or stopping their taper or adding adjuvant medications. The first 350 enrolled patients reported a high degree of choice (autonomy) in the decision to taper their opioids (median score was 9/10), as well as their readiness to taper (median readiness score was 4/5). In this and future studies, use of this approach of analyzing patients' experience of autonomy as a continuous variable will provide data essential for determining the relationship between degree of patient agency and tapering outcomes.

Among many steps to optimize patient outcomes and improve taper success, these 4 are critical: (1) adjusting the rate of taper to increase comfort; (2) using adjuvant medications, opioid rotation, or nonpharmacologic support; (3) identifying and addressing a comorbid psychiatric condition or underlying substance use disorder that requires diagnosis and treatment; and (4) identifying inadequate opioid analgesia. Patient willingness to try a taper—and their response to it—is supported with assurances that opioid doses may be restored (or increased) if pain or function deteriorates. The individual variability of pain and dysfunction require tailored dose adjustment to attain optimal pain control and overall quality of life. This patient-centered and neuroscience-informed approach avoids rigid opioid dose specifications that the CDC and Health and Human Services have cautioned against^{13,24} and remind us that our primary goal is to improve the lives of people who have pain.

Conflicts of interest statement

This version includes a change requested by the authors, ie, additional information on Dr. Fields' conflict of interest statement is now provided.

B.D. Darnall discloses that she is the principal investigator for research funding from the NIH (NIDA) and from the Patient-Centered Outcomes Research Institute (PCORI) specifically for research on opioids or opioid tapering in chronic pain (neither institute funded the current work). She is the Chief Science Advisor at AppliedVR (unrelated to the current work). She has authored 5 books on pain and opioids and receives royalties for 4. She has received consultancy fees from Axial Healthcare for developing physician education materials for safe opioid prescribing and deprescribing. She serves on the Board of Directors of the American Academy of Pain Medicine and serves on the Board of Directors for the Institute for Brain Potential. She is a scientific member of the NIH Interagency Pain Research Coordinating Committee. H.L. Fields receives compensation as scientific expert witness for opioid litigation on behalf of Janssen Pharmaceuticals.

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