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Long-Term Pain Therapy With Opioids

To the Editor The Viewpoint by Drs Bicket and Bateman highlights the asymmetry between abundant data on opioid-related harms and the scarcity of evidence regarding benefits of long-term opioid therapy for chronic pain.[1] Their analysis is timely and important. Yet an equally critical element is missing from the calculus: the harms of nontreatment.

For people with chronic pain lasting longer than 3 months who have exhausted reasonable alternatives, withholding opioids may not restore safety—it can increase risk. Chronic pain itself is strongly associated with suicidal ideation, attempts, and deaths, independent of depression or substance use.[2] Observational studies of veterans and commercial populations demonstrate that tapering or discontinuing long-term opioid therapy is associated with higher risks of overdose, mental health crises, and suicide, especially when reductions are rapid.[3,4] These are harms not of opioids themselves but of leaving pain inadequately treated.

Furthermore, patients with high-impact chronic pain have among the lowest scores on validated health-related quality-of-life instruments across chronic diseases, reflecting impairments in sleep, vitality, and social functioning.[5] For many, opioids may not produce dramatic functional gains but can make life more tolerable, reducing suffering that otherwise erodes quality of life.

The US Food and Drug Administration has rightly focused on postmarketing studies of misuse, opioid use disorder, and overdose. However, benefit-risk assessment is incomplete without parallel consideration of nontreatment harms. Regulatory frameworks should explicitly incorporate quality-of-life outcomes, patient-reported outcomes, suicidality measures, and adverse consequences of uncontrolled pain. Without this balance, clinicians are left with only half the information necessary to counsel patients.

The US has learned hard lessons about the dangers of liberal opioid prescribing. It must also acknowledge that indiscriminate restriction carries its own risks. A complete and humane regulatory science requires weighing both sides of the equation.

Lynn R. Webster, MD

Author Affiliation: Salt Lake City, Utah.

Corresponding Author: Lynn R. Webster, MD, 1285 3rd Ave, Salt Lake City, UT 84103 (lrwebstermd@gmail.com).

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In Reply We thank Dr Webster for engaging with our Viewpoint on long-term opioid therapy for pain.[1] We fully agree that high-impact chronic pain can be a source of tremendous suffering and be highly detrimental to patients' quality of life. However, Webster presumes that withholding opioids denies patients an effective therapy. Our Viewpoint highlights that the fundamental problem is the absence of high-quality evidence demonstrating benefit of initiating long-term opioid therapy for pain. Despite decades of prescribing, there remain few randomized trials beyond 12 weeks' duration and little evidence that starting long-term opioid therapy improves long-term function or quality of life compared with nonopioid or multimodal alternatives for patients with chronic pain. Presuming efficacy is not supported by the current evidence—while the risks of long-term opioid therapy are abundantly clear.

Furthermore, Webster equates not prescribing opioids with abandoning patients, which overlooks a more holistic approach to managing pain that incorporates the range of nonopioid and multimodal treatments. The question is not whether patients should receive treatment but whether starting long-term opioid therapy provides greater long-term benefit than other strategies. That comparative evidence for available treatments is still absent, leaving gaps in the data needed to guide patient-centered decisions.

Webster cites observational studies linking tapering or discontinuation of long-term opioid therapy to adverse outcomes. While we agree that data show that discontinuation has caused real harm for some patients, these data do not demonstrate that initiation of long-term opioid therapy itself improves long-term outcomes for pain. Rather, they underscore the need for safe, individualized approaches to dose reduction when tapering opioids.

We also agree that regulatory assessments should comprehensively consider patient-centered outcomes and consequences of insufficient pain relief. A central point of our

Viewpoint is the urgent need for well-designed randomized trials with placebo or active comparator groups. Such trials by design measure both treatment-related and nontreatment harms to determine whether long-term opioid therapy initiation meaningfully improves quality of life or reduces suffering compared with alternatives. The most patient-centered, scientifically rigorous, and policy-relevant course is to generate the trials needed to establish whether, and for whom, long-term opioid therapy improves outcomes compared with alternatives. Until then, regulatory frameworks, clinical guidelines, and bedside decisions will remain incomplete and rest on presumptions rather than evidence.

Mark C. Bicket, MD, PhD
Brian T. Bateman, MD, MSc

Author Affiliations: Departments of Anesthesiology and Health Management and Policy, University of Michigan, Ann Arbor (Bicket); Departments of Anesthesiology, Perioperative and Pain Medicine, and Epidemiology and Population Health, Stanford University, Palo Alto, California (Bateman).

Corresponding Author: Mark C. Bicket, MD, PhD, Department of Anesthesiology, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109 (mbicket@med.umich.edu).

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the US Food and Drug Administration.

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