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COMMENTARY

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Commentary on Lo-Ciganic *et al.*: The importance of evidence-based clinical and policy approaches to reduce opioid harms

An enduring commitment to generating and integrating evidence into policies and practices is fundamental to effectively curb the ongoing opioid epidemic. Within evolving epidemiological and structural contexts, the extent of potential impacts should be considered to maximize the benefits and minimize the burdens of interventions.

The overdose epidemic remains an urgent public health concern, with recent estimates indicating that deaths in the United States have surged to over 100 000 per year, predominantly attributed to opioids [1]. Responses to growth in opioid-involved mortality over time have emphasized opioid prescribing regulations or restrictions, including a proliferation of state laws [2] aimed at reducing harm by limiting exposure to opioids. Yet efforts to reshape medical practice are widespread, with multilevel approaches extending from federal agencies (e.g. drug labeling, prescribing guidelines) [3, 4] to individual health insurers and organizations (e.g. safety measures) [5]. Criticism of these strategies has highlighted limited evidence of their effectiveness [6] and an inability to account for differences across patients that could lead to unintended consequences. In their article, Lo-Ciganic *et al.* [7] use comprehensive methods to draw attention to an additional shortcoming of existing measures with narrow or unsupported definitions of high-risk opioid prescribing.

The authors examined concurrent use of prescription opioids and benzodiazepines using group based multi-trajectory modeling to identify patterns of medication co-prescribing based on dosage and duration. They found substantial variation in co-prescribing, resulting in nine distinct trajectories of opioid and benzodiazepine co-use. Notably, most patients were categorized into groups with low-dosage use of both medications, and over two-thirds of the sample followed trajectories with, at most, low dosages of prescription opioids (≤50 morphine milligram equivalents [MME]) and moderate dosages of benzodiazepines (≤40 diazepam milligram equivalents [DME]). Although many existing prescribing restrictions and recommendations deliberately discount treatment heterogeneity with the goal of improving overall prescribing safety, these findings indicate a need to account for additional factors beyond co-prescribing alone when implementing practice restrictions and requirements.

The study also demonstrates the value of group-based trajectory modeling (GBTM) as a tool to improve understanding of longitudinal treatment characteristics and outcomes in clinical and epidemiological research [8]. GBTM is a flexible approach for analyzing time-varying treatment measures that minimizes individual differences within a given trajectory group [8]. By capturing real rather than chance variation in estimated treatment classes, GBTM can also facilitate applications of causal inference methods in observational studies [9], enhancing its usefulness for research on treatment safety and effectiveness. Lo-Ciganic *et al.* [7] used propensity score weighting to balance characteristics across co-prescribing trajectories and estimate the association of treatment patterns with risk of subsequent opioid or benzodiazepine overdose. Elevated overdose risk was observed for groups with at least moderate opioid dosages (>50 MME) or high benzodiazepine dosages (>40 DME), comprising less than one-third of patients, but most overdoses (70%). These findings further stress the importance of considering treatment nuances in efforts to prevent adverse opioid outcomes, with strategies that grant clinical judgment to tailor prescribing to patients' needs.

Growing evidence suggests that prescribing interventions may be overly broad, creating barriers to care for patients who could benefit from medication treatment for pain and related conditions (e.g. anxiety, insomnia). Public health measures addressing opioid and benzodiazepine co-prescribing, such as national Centers for Disease Control and Prevention (CDC) prescribing guidelines [4] expected to be updated this year [10], have relied largely on epidemiologic data showing high rates of benzodiazepine involvement in opioid overdose deaths [11] and select observational studies lacking causal interpretations [12]. As the original CDC guidelines significantly influenced prescribing practices [13, 14], the revision aims to respond to concerns about the negative impact [15] and integrate current evidence [12]. The draft guidance is more moderate, suggesting extreme caution rather than avoiding co-prescribing altogether and downgrading the recommendation to acknowledge variation in patient needs and preferences that warrant greater treatment flexibility [10]. New details

also specify that risks may be larger for certain treatment regimens, such as concurrent high-dosage use [10].

Continuing to generate robust data that can be used to advance evidence-based policies and practices is critical for preventing adverse outcomes and improving the quality of health care. As part of sustained efforts to reduce opioid-related harm, actions should also be proportionate to the scope of threats to health and life. In the course of medically-supervised treatment, a minority of prescription opioid patients develop problems [16, 17], signaling the importance of focusing on high-risk clinical profiles and practices and ensuring sufficient provider discretion. Additionally, the epidemic has evolved from predominantly prescription opioid-related deaths to those involving illicit and synthetic opioids. Recognizing the enduring need to learn from earlier waves and transitions, comprehensive assessments of patients' substance use [18] alongside expanded access and delivery of opioid use disorder treatment [19] could have greater impact on currently elevated risks in an increasingly deadly drug environment.

DECLARATION OF INTERESTS

None.

KEYWORDS

Benzodiazepines, opioids, overdose, policy, practice guidelines, prescribing

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AUTHOR CONTRIBUTIONS

Hillary Samples: Conceptualization, manuscript preparation.

Hillary Samples[1,2]

[1]*Center for Pharmacoepidemiology and Treatment Science, Rutgers Institute for Health, Health Care Policy and Aging Research, New Brunswick, NJ, USA*

[2]*Department of Health Behavior, Society and Policy, Rutgers School of Public Health, Piscataway, NJ, USA*

Email: h.samples@rutgers.edu

ORCID

Hillary Samples https://orcid.org/0000-0001-5773-3705

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