HHS Public Access

Author manuscript

BMJ Qual Saf. Author manuscript; available in PMC 2024 December 14.

Published in final edited form as:

BMJ Qual Saf. ; 33(1): 1–3. doi:10.1136/bmjqs-2023-016336.

Contextualizing Opioid-Related Risk Factors before an Initial Opioid Prescription

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When asked about the similarities between the region of Valencia, Spain and the State of Oregon in the United States (U.S.), an artificial-intelligence (AI)-driven chatbot poetically listed several common features, such as natural beauty, strong focus on agricultural industries including wine production, extensive outdoor activities and a shared commitment to sustainable practices. But are there similarities in healthcare delivery, considering vastly different systems and significant practice variability, particularly regarding the management of pain and the role of opioid analgesics?

Here, the differences emerge. Oxycodone and hydrocodone are commonly prescribed opioids in Oregon (1), whereas prescribers in Valencia typically utilize tramadol and codeine (2). While Oregon has experienced a rapid increase in opioid-related deaths, reaching a record 548 (13.0 per 100,000 population) in 2021 (3), Valencia had 88 (1.8 per 100,000 population) drug-related deaths during the same period (4). Unfortunately, these gaps have begun to narrow: the annual number of patients prescribed opioids in Valencia more than doubled between 2010 and 2018 and oxycodone morphine milligram equivalents (MMEs) increased ten-fold in that time (5). Opioid-related fatalities in Spain, while still significantly lower per capita than in the U.S., also increased more than 50% between 2010 and 2017 (6).

Our comparison between Valencia and Oregon is not accidental, but rather because of two recently published studies describing opioid use in these respective regions. The first, by Garcia-Sempere and colleagues in this issue of *BMJ Quality and Safety*, describes risk factors for opioid-related misuse, poisoning and dependence in a large cohort study that included nearly all residents of Valencia, Spain (7). The region's laudable commitment to harmonizing prescription and patient outcomes data allowed the authors to identify both prescription-level and patient-level risk factors for developing serious opioid-related harms after an initial opioid prescription. Of nearly a million patients who initiated opioid

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Contributors: SGW and JAH both contributed to the conceptualisation, drafting and critical revision of the manuscript.

Patient consent for publication: Not required.

Ethics approval: Not applicable.

analgesics, about 2 of every 1,000 had a serious opioid-related outcome. Several patient-level factors were associated with higher risk, such as male sex, those with comorbidities, and younger patients (ages 18-44 years).

The second paper, by Weiner, et al, conducted a similar analysis of risk factors for opioid overdose after an initial opioid prescription utilizing linked data from Oregon (8). As a result of the fragmented U.S. health system, the linking procedure was more complex and excluded uninsured patients (9). Similar to the Spanish study, about 3 of every 1,000 patients suffered an overdose. In the U.S. study patients who were male, older (75 years or greater), had public insurance (i.e., Medicaid and/or Medicare), had comorbidities, and had concurrent substance use disorder or depression were at greater risk of subsequent non-fatal and fatal overdose.

Comparing and contrasting these two studies is helpful and important. Both used a linked dataset on a population level to determine future opioid-related risk after an initial opioid prescription, as even a first opioid prescription can portend chronic use and even opioid use disorder (10–12). In the Valencia study, codeine was the “safest” medication, followed by tramadol, whereas short-acting opioids such as oxycodone had a nearly five-fold increased risk (vs tramadol). In the Oregon study, codeine was again associated with fewer events, but tramadol had a higher risk (adjusted hazard ratio (aHR) 2.8) compared with oxycodone (aHR 1.7). Both studies showed increased harm with concurrent use of opioids and benzodiazepines. Unexpectedly, the use of long-acting formulations and higher MMEs were not associated with increased risk in Oregon but were in Valencia. The impact of patents’ social determinants of health measures was similar: in Valencia, those who lacked economic resources had a 2.1-fold increased HR, while in Oregon, those with Medicaid – an insurance type reserved for those with limited income - were strong risk factors (aHR 3.8) for subsequent opioid-related adverse outcomes.

What are clinicians to make of this hodgepodge of risk factors? Are the younger or older at risk? Is tramadol safe or should it be avoided, especially when it has been associated with higher risk of prolonged opioid use when compared with other short-acting opioids (13)? Perhaps the role of codeine as an analgesic should be revisited? It has been reported to achieve equivalent analgesia to oxycodone both in emergency department treatment of acute pain (14) and after surgically managed fractures (15). Yet, how do we account for the significant heterogeneity in the CYP2D6 gene responsible for codeine metabolism that can markedly vary amongst individuals (16)?

The results beg the ultimate question: “now what”? The Valencia authors conclude: “by identifying individuals at greatest risk, as well as prescription patterns associated with greater risk…these findings may provide guidance to clinicians, healthcare managers and policymakers to improve the safety of the therapeutic management of non-cancer pain.” Likewise, the Oregon study concludes: “these findings may also be used by researchers to develop clinical decision-making tools, and policymakers and insurers may use the data to provide opioid prevention and treatment resources to individuals who are at greatest risk for opioid overdose.”

Herein, we recommend caution and contextualization, particularly in light of the conclusions that varied between the studies and administrative data that were neither prospectively collected nor inclusive of patient-reported outcomes. The first point to highlight: even though there is risk, the rate of 2-3 opioid-related outcomes per 1,000 patients may be an acceptable risk to some patients and prescribers. The second point is that the best way to avoid complications from opioids is to avoid exposure whenever possible. Multimodal analgesia including non-steroidal anti-inflammatory medications, acetaminophen (paracetamol), topical medications and local anesthetics are often sufficient to address acute pain without exposing patients to the attendant downstream risks of opioids (17). Thirdly, differences between studies may be due to local practices and other undetected social determinants of health, so any criteria used to limit prescriptions should consider specific patient populations.

If a trial of opioids is considered, recommendations from guidelines such as by the U.S. Centers for Disease Control and Prevention (18) or guidelines from Spain's Socidroalcohol (19) should be incorporated. There are few situations in which an initial opioid prescription should be written for more than a few days, during which time the most severe acute pain can be addressed while minimizing the risk of physiological dependence and related increase in the risk of addiction. Initial prescriptions for more than a few days should be a rare exception. Likewise, these two studies align with multiple studies that demonstrate the risks of concurrent opioid and benzodiazepine prescriptions. So, co-prescribing of sedatives with opioids should be avoided, and patients who are already on benzodiazepines should be advised not to take their benzodiazepine during the few days that the opioids are used for acute pain. Finally, long-acting opioids should essentially never be prescribed for acute pain, another finding corroborated by multiple studies including this new study from Valencia.

An overarching challenge is how to implement these findings into routine care. Implementation science and practice change management can help identify interventions to facilitate best practices, but can these established approaches keep up with rapidly advancing technology and data? What happens when the aforementioned AI-driven chatbot begins to suggest and/or make medical decisions? Will patients be inadvertently harmed or asked to suffer greater levels of pain because of studies that had disparate results and were conducted in different populations? Will there be unintended consequences such as perpetuating long-standing disparities in pain management (20)?

Ultimately, it will be up to the prescriber and patient dyad to understand risk tolerance and navigate these important decisions together. The importance of using shared decision-making risk/benefit discussions has been highlighted in the updated 2022 CDC opioid prescribing guidelines (18). Unfortunately, operationalization of these discussions within provider workflows is not well described. Given the ever-increasing expectations and time constraints for medical visits, appropriate resources and reliable technology solutions are urgently needed to integrate the rapidly expanding knowledge database to provide both clinicians and patients with the tools to balance appropriate pain management and opioid safety.

Funding:

Dr. Weiner reports support from National Institutes of Health grants 5-R01-DA044167 and 5-R01-HS026753 related to this work.

Competing interests:

Dr. Weiner reported receiving personal fees from Vertex Pharmaceuticals, Inc, and Cessation Therapeutics, Inc; and grants from National Institute on Drug Abuse, Foundation for Opioid Response Efforts, and Elevance Health Foundation outside the submitted work. Dr Hoppe reported receiving grants from the National Institute of Drug Abuse, the Bureau of Justice Assistance, and the Substance Abuse and Mental Health Services Administration outside the submitted work.

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