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Invited Commentary

Legalization of Medical Marijuana and Incidence of Opioid Mortality

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The rapid acceleration of prescription opioid-related overdose deaths in the United States is correlated with the availability of stronger opioid medications, as well as a change in medical practice from withholding opioid medication because of dependence risk[1] to treating patients with chronic pain with opioids. Subsequently, the pendulum of concern has swung again, driven by the public health crisis of rising opioid analgesic addiction, overdose, and death. Opioid medications are problematic as a treatment for chronic pain. Opioid pharmaceuticals cause other adverse effects when used for long periods, such as tolerance, hyperalgesia, and gastrointestinal complications, making this class of drugs a poor choice for long-term use. As is well known, prescription opioids also have great abuse potential due to their influence on stress and reward circuits in the brain, promoting nonmedical use and abuse and diversion of prescription medications.

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In this issue, Bachhuber et al[2] examine the link between medical marijuana laws and unintentional overdose mortality in which an opioid analgesic was identified. Using Centers for Disease Control and Prevention data, states with and without medical marijuana laws were contrasted for age-adjusted, opioid-related mortality. Overall, the incidence of opioid analgesic-associated mortality rose dramatically across the study period (1999-2010). States with medical marijuana laws had higher overdose rates than did those without such laws when population-adjusted mortality was analyzed across years, although the rise in deaths over the study period was similar for both groups. In contrast, a convincing protective effect of medical marijuana laws was found in a covariate-adjusted, time-series model in which opioid analgesic mortality declined steadily based on years since medical marijuana laws were enacted, termed *implementation*. The model included an analysis of the impact of critical policies for prescription opioid regulatory efforts: prescription monitoring programs, pharmacist collection of patient information, state and oversight of pain management clinics, as well as state unemployment rates. In states with medical marijuana laws, age-adjusted overdose deaths in which opioids were present declined in yearly estimates since medical marijuana law implementation. Indeed, across the 13 states that approved medical marijuana laws in the study period, the decline in opioid overdose mortality strengthened over time, achieving a mean decline of 24.8%. Worthy of note, a weak contribution was found for state oversight policies such as prescription monitoring and pain management clinics; this finding has been reported previously.[3] The striking implication is that medical marijuana laws, when implemented, may represent a promising approach for stemming runaway rates of nonintentional opioid analgesic-related deaths. If true, this finding upsets the applecart of conventional wisdom regarding the public health implications of marijuana legalization and medicinal usefulness.

The difficulty in endorsing the medical marijuana protective hypothesis is that medical marijuana laws are heterogeneous across states, engender controversy in state legisla-

tures, and produce varied approaches.[4] Bachhuber et al[2] arguably capture this best in the implementation time-lag measure. Once medical marijuana laws are passed, states struggle to develop policies for patient eligibility and access but universally accept chronic pain as the most appropriate medical condition. Federal enforcement agencies (who list marijuana as a Schedule I drug with no medical value) challenge states during implementation, most commonly when distribution centers or dispensaries are authorized as a solution to patient access. The cross-state variability in the implementation variable and its dynamic changing nature make it hard to define what the implementation proxy is measuring. The assumption that improvement in medical marijuana access policies occurs gradually, as patients with pain become enrolled over time, is reasonable. What is novel in the contribution of Bachhuber et al[2] is the suggestion that what is being tracked is an evolving drug policy that may mitigate the secular rise in opioid analgesic-related deaths.

If medical marijuana laws afford a protective effect, it is not clear why. If the decline in opioid analgesic-related overdose deaths is explained, as claimed by the authors, by increased access to medical marijuana as an adjuvant medication for patients taking prescription opioids, does this mean that marijuana provides improved pain control that decreases opioid dosing to safer levels? Research[5] supports the hypothesis that cannabinoid receptors (CB1 and CB2) operate as a parallel, independent analgesic system. Endogenous cannabinoids block pain signals in pain centers such as the periaqueductal gray, and decrease activation in the locus coeruleus, which regulates sympathetic activation during stress. Preclinical and clinical trial pharmacologic studies[6,7] have shown independent analgesic action of medical marijuana and augmented analgesia when a cannabinoid CB1 agonist is added to an opioid background.

In the present study,[2] the authors stress that approximately 60% of the decedents possessed a valid opioid analgesic prescription from a single provider. Although the epidemiologic data sources are robust and the time-series approach is convincing, it is unlikely that improved pain control with the use of marijuana in patients with chronic pain is the primary driver for the observed decline in opioid overdose. Indeed, the remaining 40% of the decedents in this cohort without a valid opioid prescription were not likely patients with pain. The report provides no information on the health history of the decedents with or without valid prescriptions, such as a history of multiple providers, comorbid polypharmacy, and poor health (eg, obesity), which are associated with overdose mortality.

Opioid overdose–associated mortality in the group without a valid prescription is likely related to opiate and polydrug/alcohol addiction developed through recreational abuse, most often presaged by longstanding psychiatric illness. In a recent study[8] of past-year, nonmedical prescription opioid use, individuals with abuse or dependence were more likely to have psychiatric symptoms, such as panic and agoraphobia, report poor health, have misused another class of prescription medication, used heroin, and initiated substance use before age 13. In Maine, where the rates of opioid analgesic overdose deaths are high, addiction and related psychiatric disorders represent an estimated 50% of opioid analgesic-related deaths.[9] Increased access to medical-grade marijuana, procured legally or illegally, may offer an alternative intoxicant that may compete with opiate misuse and, thereby, be similarly protective. Preclinical and imaging studies[10] have established that the psychogenic "pain" of psychiatric illness, which often leads to drug and alcohol abuse and addiction, operates through the same neural circuits as pain generated by other medical conditions. Both opioids and cannabinoids independently reduce stress reactivity and increase dopamine-mediated reward. Hence, medical marijuana use may similarly lessen the drive to use opiates at lethal levels in individuals with nonpain, psychiatric conditions who have psychotropic medications as a frequent concomitant of exposure at the time of death. It is also possible that for some, medical marijuana is a substitute for opioids, rather than an adjuvant. The potential protective role of medical marijuana in opioid analgesic-associated mortality and its implication for public policy is a fruitful area for future work.

ARTICLE INFORMATION

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