For Opioid Overdose Survivors, One Treatment May Reduce Risk of Death Over Another

— Study suggests modest difference, but outside experts question results

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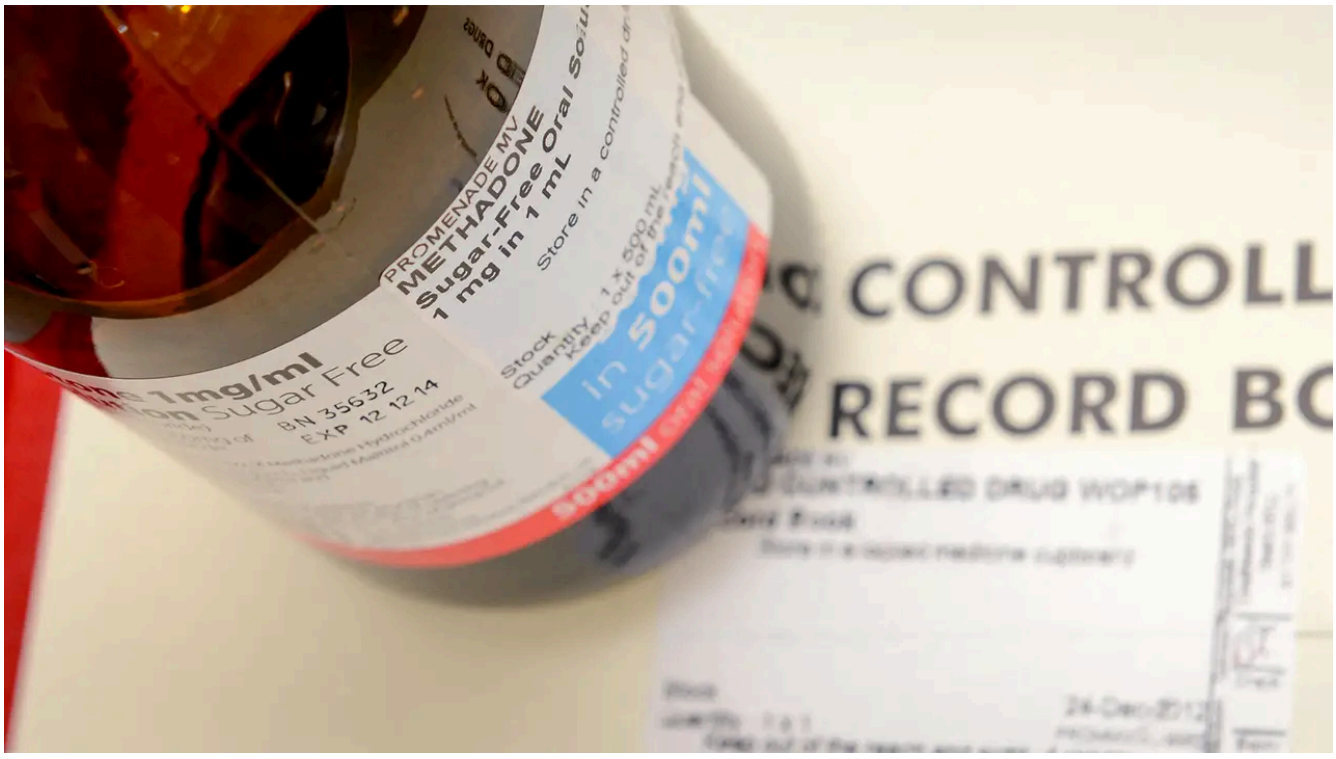

Key Takeaways

- People who experience an opioid overdose are at greater risk of death, but data on which opioid agonist treatments are most effective in supporting this high-risk population are limited.
- In a retrospective cohort study of opioid overdose survivors, starting methadone was associated with a reduced risk of death during the subsequent year compared with starting buprenorphine-naloxone.
- In an accompanying commentary, experts questioned whether methadone is truly "intrinsically superior" to buprenorphine-naloxone.

For opioid overdose survivors, starting methadone was associated with a reduced risk of death during the subsequent year compared with starting buprenorphine-naloxone, a retrospective cohort study from Canada suggested.

Using a target trial emulation among over 5,800 individuals with past-year opioid overdose, 5.6% of those who started methadone died within 1 year compared with 7.1% of those who started buprenorphine-naloxone (HR 0.78, 95% CI 0.63-0.95, *P*=0.01), reported Robert A. Kleinman, MD, MSc, of the Center for Addiction and Mental Health in Toronto, and co-authors.

Of the 375 individuals who died within 1 year, opioid overdose was identified as a cause of death in 264. Of those who started on methadone, 3.8% died of an opioid overdose versus 5.1% of those in the buprenorphine-naloxone group, they reported in *JAMA Network Open*.

Median time to treatment discontinuation was 25 days in the methadone group compared with 16 days in the buprenorphine-naloxone group (HR 0.78, 95% CI 0.74-0.82, *P*<0.001). However, the time to first opioid overdose did not significantly differ between groups (HR 1.07, 95% CI 0.97-1.18).

People who experience an opioid overdose are at greater risk of death, but data on which opioid agonist treatments are most effective in supporting this high-risk population are limited, Kleinman and co-authors noted.

"The short treatment durations, high rates of mortality, and repeat opioid overdose among this group of individuals who started recommended treatments for [opioid use disorder] highlight the importance of improving treatment outcomes in this high-risk group," they concluded. "Epidemiologic studies and pragmatic trials in other jurisdictions are needed to confirm these findings and further evaluate outcomes in this high-risk population."

In an accompanying commentary, Evan Wood, MD, PhD, of the University of British Columbia in Vancouver, and Leen Naji, MD, PhD, of the University of Arizona in Tucson, threw cold water on the finding that methadone may confer a survival benefit over buprenorphine-naltrexone after overdose.

"Weakening the inference that methadone is intrinsically superior" was the finding that buprenorphine-naloxone was linked to a lower risk of overdose while treatment was being received, they noted, pointing to per-protocol analyses that showed no significant difference in the hazard of death among those starting methadone and buprenorphine-naloxone (HR 0.84, 95% CI 0.48-1.47), and a greater hazard of opioid overdose among those starting methadone (HR 1.52, 95% CI 1.19-1.93, *P*<0.001).

Moreover, no mortality difference was observed among individuals without opioid agonist treatment exposure in the preceding 3 years (HR 1.00, 95% CI 0.67-1.50).

"The most noteworthy finding of the study ... may not be the potential modest relative differences between medications, but rather the persistently poor outcomes observed among overdose survivors regardless of treatment choice," Wood and Naji wrote. "Approximately 6% of participants died within 1 year, more than one-quarter experienced another overdose, and nearly 90% discontinued treatment during follow-up."

Researchers and policymakers should stop debating the "relative merits" of different kinds of opioid agonist treatments and instead focus on "why initiating and remaining on [this treatment] is so unattractive to most patients," they argued.

This retrospective cohort study with target trial emulation included individuals who started methadone or buprenorphine-naloxone treatment from January 2017 through December 2023 in Ontario, Canada. Participants had a past-year emergency department visit for an opioid overdose and no use of either medication for 7 days. Those starting each medication were matched on a 1:1 basis using propensity scores, sex, and index date.

Of the 5,882 people included in the study, mean age was 35.8, and 67.9% were male. Among matched participants, 56.6% had received opioid agonist treatment in the past 3 years, and 44.7% had received methadone.

Wood and Naji noted that "confirmation in other settings may be valuable" since generalizability may be limited by the fact that approximately 40% of eligible individuals were excluded after propensity score matching.

Shannon Firth has been reporting on health policy as MedPage Today's Washington correspondent since 2014. She is also a member of the site's Enterprise & Investigative Reporting team. Connect:

Disclosures

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Kleinman reported receiving grants from the University of Toronto Department of Psychiatry Academic Scholar Award, the Innovation Fund of the Alternative Funding Plan of the Academic Health Sciences Centres of Ontario, and the Centre for Addiction and Mental Health Foundation, and holding stock in Pfizer and Novo Nordisk.

A co-author reported a relationship with the Fonds de recherche du Québec Santé.

Wood reported relationships with Vancouver Coastal Health, the Canadian Institutes of Health Research, the National Institute on Drug Abuse, the Canadian Research Initiative in Substance Misuse, Numinus Wellness, and the Canadian Medical Protective Association. Naji reported no conflicts of interest.

Primary Source

JAMA Network Open

Source Reference: Kleinman RA, et al "Methadone vs buprenorphine-naloxone in opioid overdose survivors" JAMA Netw Open 2026; DOI: 10.1001/jamanetworkopen.2026.29313.

Secondary Source

JAMA Network Open

Source Reference: Wood E, Naji L "Discerning the forest from the trees when comparing treatments for opioid use disorder" JAMA Netw Open 2026; DOI: 10.1001/jamanetworkopen.2026.29640.