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COMMENTARY

Potential Risk Window for Opioid Overdose Related to Treatment with Extended-Release Injectable Naltrexone

Ingrid A. Binswanger[1,2,3] · **Jason M. Glanz**[1,4]

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Extended-release (ER) injectable naltrexone (Vivitrol®) is a monthly injection approved for the treatment of opioid use disorder in the US. Other treatments for opioid use disorder include opioid agonists or partial agonists such as methadone and buprenorphine-containing products (e.g. buprenorphine-naloxone). As an opioid antagonist, naltrexone blocks the euphoric effects of opioids and may reduce the risk of opioid overdose once individuals are successfully induced into treatment [1]. However, paradoxically, the risk of opioid overdose may increase if individuals try to challenge the opioid blockade associated with naltrexone [2]. Two recent studies raise concerns about the susceptibility to opioid overdose associated with ER injectable naltrexone. In a randomized trial (n=570) comparing the effectiveness of buprenorphine-naloxone with ER injectable naltrexone, 15 individuals had 18 overdose events in the ER injectable naltrexone arm, compared with 8 individuals who had 10 overdose events in the buprenorphine-naloxone group; the difference in the number of individuals with events was reported to be not statistically significant (p=0.14), but the relative proportion of individuals with overdoses was nonetheless concerning (5.3% vs. 2.8%) [3]. An observational study in Western Australia demonstrated an elevated risk of fatal overdose among men treated with a different formulation of ER naltrexone (implant naltrexone), relative to men treated with methadone, but there was no difference when men and women were combined [4]. Overall, prior data about overdose risk associated with extended-release naltrexone is difficult to interpret due to inconsistent and poorly described procedures for ascertaining overdoses across studies [5].

A prior study also noted overdose events after discontinuing treatment with ER injectable naltrexone [3], perhaps due to loss of tolerance during treatment. Other medications for opioid use disorder are associated with an elevated risk of overdose after treatment discontinuation relative to on-treatment periods [3, 6]. This post-treatment overdose risk may be exacerbated if naltrexone results in upregulation of mu receptors, as suggested by animal studies [7, 8]. At present, there is a paucity of data comparing the post-treatment safety of ER injectable naltrexone with the post-treatment risk of methadone and buprenorphine. Safety data would help clinicians and patients make informed decisions among treatment options.

Future postmarket safety studies should compare the risk of fatal and nonfatal overdose among cohorts of patients who received ER injectable naltrexone, methadone, or buprenorphine. However, studying the effects of opioid use disorder medication treatments on susceptibility to opioid overdose poses numerous methodological challenges. Since overdose is a relatively uncommon event, prospective cohort studies may be cost prohibitive since they would require sizeable study populations to achieve adequate power. Loss to follow-up for individuals with opioid use disorder is frequent and often informative (i.e. individuals who are lost to follow-up are also more likely to experience the outcome). In addition, there may be confounding by indication, where the clinical indication for choosing a specific treatment for an individual is also associated with the outcome. Retrospective studies relying on International Classification of Disease codes extracted from large medical claims or electronic health record databases are subject to misclassification bias since these data are collected for clinical care and billing rather than for research purposes. To address these challenges, observational safety studies

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✉ Ingrid A. Binswanger
Ingrid.A.Binswanger@kp.org

1 Institute for Health Research, Kaiser Permanente Colorado, PO Box 378066, Denver, CO 80237-8066, USA

2 Colorado Permanente Medical Group, Aurora, CO, USA

3 Division of General Internal Medicine, University of Colorado School of Medicine, Aurora, CO, USA

4 Colorado School of Public Health, Aurora, CO, USA

would require large denominated populations of patients treated with opioid use disorder medications, adequate follow-up, capture of potential confounding variables, and the ability to conduct medical record review to confirm exposures and outcomes. As part of the medical record review, it would be important to use a rigorous, standardized definition of fatal and nonfatal overdose so that results can be compared across study settings.

Another important challenge is determining the appropriate exposure period during which an opioid overdose event could be attributed to direct or indirect effects of the treatment medication. To help identify appropriate on-treatment and post-treatment windows to guide future safety studies, Saucier and colleagues investigated fatal opioid overdoses potentially associated with the ER injectable suspension of naltrexone [9]. They reviewed available documentation on potential opioid overdose fatalities that occurred after exposure to ER injectable naltrexone. These data were derived from spontaneous reports to the US FDA Adverse Event Reporting System (FAERS). Of 263 potential overdose deaths identified, 52 cases had exposure to ER injectable naltrexone for opioid use disorder. Among those whose last naltrexone administration date was known ($n=28$), approximately 18% ($n=5$) were receiving treatment (i.e. within 28 days of the last injection), 61% ($n=17$) occurred after 28 days but before 2 months, and 21% ($n=6$) occurred later [9]. These hypothesis-generating data suggest that there may be a 1-month post-treatment exposure window during which individuals are at high risk for opioid overdose.

If a future controlled study identifies an increased risk for opioid overdose within the hypothesized exposure window, the results need to be interpreted in context. For example, it is possible that, even though ER injectable naltrexone could increase post-treatment susceptibility to overdose, it may prevent more overdose than it causes due to on-treatment protective effects, i.e. the benefits outweigh the risks. Given that there are alternative effective treatments, the relative effectiveness of ER injectable naltrexone compared with other treatments should be considered. An increased risk should also be interpreted in the context of accessibility, cost, convenience, and adherence. If ER injectable naltrexone is selected as the treatment of choice after weighing its risks and benefits, it should be administered with naloxone, and instruction given on how to prevent and treat an opioid overdose [10].

As the current opioid epidemic in the US continues to intensify [11], the use of ER injectable naltrexone and other medications to treat opioid use disorders is likely to increase. While widespread use of these treatments could significantly reduce the morbidity and mortality associated with opioid use disorders, each treatment will have a different risk–benefit ratio for an individual patient. Given that overdose is a serious, life-threatening event, well-designed medication safety studies can help inform these complex clinical decisions.

Compliance with Ethical Standards

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