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

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Extended-release injectable naltrexone (Vivitrol®) is a monthly injection approved for the treatment of opioid use disorder in the United States. 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 onto treatment [1]. Paradoxically, however, 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 extended-release naltrexone. In a randomized trial (n=570) comparing the effectiveness of buprenorphine-naloxone with extended-release naltrexone, 15 individuals had 18 overdose events in the injectable naltrexone arm compared to 8 individuals who had 10 overdose events in the buprenorphine-naloxone group; the difference in 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 extended-release 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].

Prior studies have also noted increased rates of overdose after discontinuing treatment with extended release naltrexone [3], likely due to loss of tolerance during treatment. Other

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medications for opioid use disorder are associated with an elevated risk of overdose after treatment discontinuation relative to on-treatment periods [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 injectable naltrexone to post-treatment risk of methadone and buprenorphine. Safety data would help clinicians and patients make informed decisions among treatment options.

Future post-market safety studies should compare the risk of fatal and nonfatal overdose among cohorts of patients who received 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 sizable 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 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 is also 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 with 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 extended-release injectable suspension of naltrexone [9]. Saucier and colleagues reviewed available documentation on potential opioid overdose fatalities which occurred after exposure to injectable naltrexone. These data were derived from spontaneous reports to the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). Out of 263 potential overdose deaths identified, 52 cases had exposure to injectable naltrexone for opioid use disorder. Among those whose last naltrexone administration date was known (n=28), approximately 18% (n=5) were on treatment (i.e., within 28 days of the last injection), 61% (n=17) occurred after 28 days but before two months, and 21% (n=6) occurred later [9]. These hypothesis-generating data suggest that there may be a one -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 windows, the results need to be interpreted in context. For example,

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it is possible that, even though extended-release 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 injectable naltrexone compared to other treatments should be considered. An increased risk should also be interpreted in the context of the accessibility, cost, convenience, and adherence. If injectable naltrexone is selected as the treatment of choice after weighing its risks and benefits, it should be given with naloxone and instruction on how to prevent and treat an opioid overdose [10].

As the current opioid epidemic in the United States continues to intensify [11], the use of extended-release 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.

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