



September 2019

### An Approach to Evaluate the Effects of Concomitant Prescribing of Opioids and Benzodiazepines on Veteran Deaths and Suicides

Compared to the civilian population, veterans have higher rates of chronic pain, traumatic brain injury, post-traumatic stress disorder, depression, substance use disorder, and other mental health conditions, due to the effects of active duty and combat-related injuries. Veterans may be prescribed opioids (for pain) and benzodiazepines (for anxiety or insomnia). Overdoses and fatalities are of particular concern when opioids and benzodiazepines are prescribed concurrently.

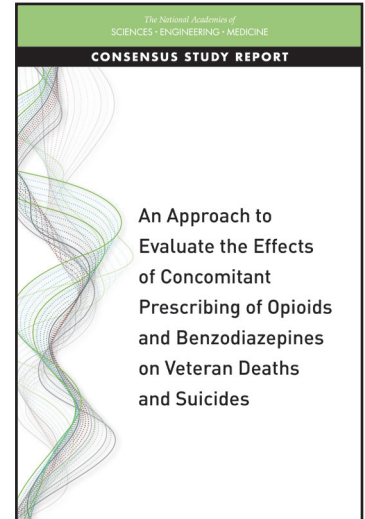
Responding to the concern about opioid and benzodiazepine use in the veteran population, the U.S. Department of Veterans Affairs (VA) asked the National Academies of Sciences, Engineering, and Medicine to “develop a protocol/study design to evaluate the relationship between concomitant opioid and benzodiazepine medication practices at the VA, for treating mental health and combat-related trauma, which potentially led to veteran’s deaths and suicides.”

In the resulting report, *An Approach to Evaluate the Effects of Concomitant Prescribing of Opioids and Benzodiazepines on Veteran Deaths and Suicides*, the committee developed study designs focusing on the following overarching research question: What were the effects of (1) opioid initiation and (2) tapering (i.e., discontinuing or reducing opioid dosage) strategies in the presence of benzodiazepines in veterans on all-cause mortality and suicide mortality from 2010 to 2017?

A randomized trial is the ideal method for answering causal questions about the comparative effectiveness and safety of medical treatments. The committee acknowledges that it would neither be ethical nor feasible to conduct a randomized controlled trial (RCT) to answer the above research question. The report describes two hypothetical randomized trials and how they could be emulated (i.e., closely approximated) using historical data to evaluate the relationship between co-prescribing of opioids and benzodiazepines and veterans’ deaths and suicides between 2010 and 2017.

#### EMULATING THE HYPOTHETICAL TRIALS USING HISTORICAL DATA

Data from various VA databases, such as VA pharmacy data and the VA Suicide Prevention Applications Network database, could be used for studies that emulate the hypothetical trials. For instance, VA pharmacy data includes information on prescriptions filled and dispensed to VA patients. The VA’s Corporate Data Warehouse contains multiple databases that could provide information on, for example, demographic characteristics, clinical diagnoses, and treatments. Additionally, the VA Suicide Prevention Applications Network database can be used to identify non-fatal suicide events (e.g., suicide attempts, serious suicidal ideation). Other potential data sources include the Centers for Disease Control and Prevention’s National Death Index.



## HYPOTHETICAL TRIALS

In the hypothetical initiation trial, researchers would study the effects of starting an opioid for chronic pain and its relationship to veterans' mortality. Veterans with a chronic pain diagnosis who are taking benzodiazepines would be randomly assigned into one of two treatment strategies and followed for 18 months:

- Initiation of treatment with an opioid and continuation for one year, unless not tolerated by the participant
- Initiation of treatment with a non-aspirin non-steroidal anti-inflammatory drug (NSAID) and continuation for one year, unless not tolerated by the participant

Providers usually decide to taper opioids to prevent long-term opioid-related risks or medication misuse. However, tapering a patient who is tolerant to opioids may actually contribute to adverse consequences, including suicide. In the hypothetical tapering trial, veterans would be eligible after their prescribed daily opioid dosage reaches a level that would be likely to induce opioid dependence. Treatment strategies, to which the veterans would be randomly assigned and followed for six months or until an outcome of interest occurs, include:

- No opioid dosage reduction: Continue opioid dosage at the same level (or less than 5 percent reduction)
- Slow dosage reduction: Reduce dosage by 5 to 10 percent per month on average over three months
- Moderate to fast dosage reduction: Continue treatment but reduce dosage by more than 10 percent in a month
- Abrupt discontinuation: Stop taking opioids completely

The outcomes of interest for both hypothetical trials were all-cause mortality and suicide mortality.

## CONCLUSION

Any related investigations using existing data would be an excellent opportunity to use the wealth of clinical information in the VA medical records databases to clarify the connections between important clinical conditions, changes in opioid and benzodiazepine prescribing practices over the years 2010–2017, and outcomes. They might also reveal important insights into pain treatment practices that could inform the use of opioid treatment as part of chronic pain management in the future.

## Committee on Developing a Protocol to Evaluate the Concomitant Prescribing of Opioids and Benzodiazepine Medications and Veteran Deaths and Suicides

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