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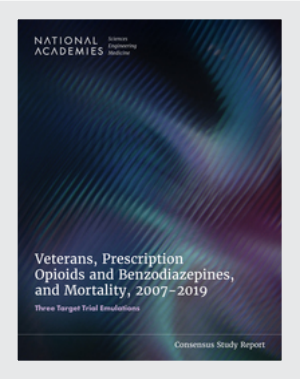

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019

Three Target Trial Emulations

Brian L. Strom and Donna Almario Doebler, *Editors*

Committee on Evaluating the Effects of Opioids and Benzodiazepines on All-Cause Mortality in Veterans

Board on Population Health and Public Health Practice

Health and Medicine Division

Consensus Study Report

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Reviewers

This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **LINDA C. DEGUTIS,** Yale School of Public Health, and **DAN G. BLAZER, II,** Duke University Medical Center. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

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Acknowledgments

Many people were critical in helping the committee complete this report and accomplish its charge. The committee sincerely appreciates the speakers at its public meetings, whose participation ensured that our public meetings would include a collection of relevant and diverse viewpoints, which allowed us to learn about Department of Veterans Affairs policies, and prescribing practices surrounding opioids and benzodiazepines, as well as the effects of their co-prescribing, which were central to our charge.

The committee is also grateful for the support provided by our Westat consultants: Joseph Gasper, Jennifer Edwards, Anne Roubal, Chris Manglitz, Sherrie Ji, and Carina Tornow. Additionally, the committee's work benefited from consultation with the University of Pennsylvania's Center for Evidence Based Practice with Nikhil Mull, Brian Leas, and Shazia Mehmood Siddique regarding existing literature on opioid tapering practices and its effects on mortality.

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Contents

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

APPENDIXES

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Boxes, Figures, and Tables

BOXES

FIGURES

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLES

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

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Preface

Prescribing patterns for opioids and benzodiazepines, and the outcomes associated with the use of these medications, especially in the veteran population, have been of long-standing concern to researchers and policy makers alike. Recent questions have raised concerns that the concomitant use of these medications may be contributing to increased mortality via a variety of pathways of action. To address these questions, the National Academies of Sciences, Engineering, and Medicine (the National Academies) Committee on Evaluating the Effects of Opioids and Benzodiazepines on All-Cause Mortality in Veterans was charged with doing the new analyses needed to determine the effects of opioid and benzodiazepine prescribing on the risk of death among veterans who received care from the Department of Veterans Affairs (VA) between 2007 and 2019. The wide scope, practical challenges, and far-reaching consequences of addressing this question presented a humbling prospect for me and my fellow committee members.

The committee's deliberations also touched on other questions and topics of public health significance, such as the difficulty in measuring the access to and use of unprescribed opioid and benzodiazepines and a lack of dialogue between data sources concerning veterans' access to medications. Ultimately, we could only accept that these challenges are insurmountable in the context of these analyses and address them analytically and in our stated limitations.

To begin to accomplish our charge and ensure that our deliberations were well informed, in addition to drawing on published literature, we heard from a variety of expert speakers, veterans, and veteran advocates. The public was also free to submit testimony to the committee. In its closed sessions, the committee deliberated on the design recommendations from the 2019 report on this same topic and worked to identify the best strategies to address adequately its charge while working around the analytical obstacles presented to it. Ultimately, the committee met over 11 times to deliberate on the design and later the results and met regularly in smaller groups to prepare this report.

We are greatly appreciative of the support provided by the study staff, who worked tirelessly over many months to support our deliberations and report writing. The committee would like to specifically thank Donna Almario Doebler, who served as study director and provided both assistance and direction to the committee's work, and Rose Marie Martinez, for her insight and feedback on the report. Other members of the National Academies staff who supported this study include Aashaka Shinde, Emma Fletcher, Mia Saltrelli, and Grace Reading. We would

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

also like to thank Anne Roubal, Jennifer Edwards, and Joseph Gasper from Westat. The committee would also like to acknowledge Amanda Borsky, Jenifer Stelmack, and Lolita Kachay at the VA for facilitating data access.

Last, as committee chair, I would especially like to thank my colleagues, many of whom are first-time National Academies committee members, for serving as an exceptional team, and sharing their time and expertise for this project over almost 3 years. They put in tremendous work and creative and careful methodologic and clinical insight, providing drafts of the report text and critiquing each other's work to ensure that the report was concise, and the methods used were at the cutting edge of research.

Brian L. Strom, *Chair*
Committee on Evaluating the Effects of Opioids and
Benzodiazepines on All-Cause Mortality in Veterans

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Acronyms and Abbreviations

ADE	adverse drug events
aIRR	adjusted incidence rate ratio
aOR	adjusted odds ratio
aRR	adjusted risk ratio
ASMD	absolute standardized mean difference
CARA	Comprehensive Addiction and Recovery Act
CBT	cognitive behavioral therapy
CDC	Centers for Disease Control and Prevention
CDW	VA Corporate Data Warehouse
CE	continuing education
CEP	Center for Evidenced-Based Practice
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
CNS	central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CPG	Clinical Practice Guideline
CPT	current procedural terminology
DoD	Department of Defense
Dx	diagnosis
ED	emergency department
EHR	electronic health record
ESRD	End Stage Renal Disease
FDA	U.S. Food and Drug Administration

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GAD	Generalized Anxiety Disorder
HHS	U.S. Department of Health and Human Services
HR	hazards ratio
HSR	health systems research
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
IOM	Institute of Medicine
IPTW	inverse probability of treatment weights
ITT	intent-to-treat
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
LAAM	Levo-Alpha Acetyl Methadol
LTOT	long term opioid treatment/therapy
MME	morphine milligram equivalents
mOR	matched odds ratio
MOUD	medication for opioid use disorder
MRI	magnetic resonance imaging
NCHS	National Center for Health Statistics
NDI	national death index
NHANES	National Health and Nutrition Examination Survey
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NSAIDS	non-steroidal anti-inflammatory drugs
OA REMS	opioid analgesic risk evaluation and mitigation strategy
OSA	obstructive sleep apnea
OSI	Opioid Safety Initiative
OUD	opioid use disorder
PDMP	Prescription Drug Monitoring Program
PS	propensity score
PTSD	post-traumatic stress disorder
QC	quality control
RCT	randomized controlled trial
REMS	risk evaluation and mitigation strategy
ROBINS-I	risk of bias in non-randomized studies—of interventions
RR	risk ratio
Rx	prescription
SD	standard deviation
SE	standard error
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSN	Social Security number

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SUD	substance use disorder
SUPPORT	Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act
TCA	tricyclic antidepressant
TeCA	tetracyclic antidepressant
TTE	target trial emulation
USVETS	United States Veterans Eligibility Trends and Statistics
VA	Department of Veterans Affairs
VCCP	Veterans Community Care Program
VCP	Veterans Choice Program
VEP	Veteran Engagement Panel
VHA	Veterans Health Administration
VINCI	VA Informatics and Computing Infrastructure
VISN	Veterans Integrated Service Network

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Abstract

Deaths associated with the co-prescribing of opioid and benzodiazepine pharmacotherapies have raised concerns among health care providers, federal agencies, and the public. The U.S. Congress has expressed concerns particularly about this issue in the veteran population. Veterans are more likely than non-veterans to experience pain, trauma, and mental health conditions from training and combat-related service and be prescribed pharmacotherapies for treatment. Congress mandated that the Department of Veterans Affairs (VA) request an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (the National Academies) be assembled to evaluate the effects of prescribed opioid and benzodiazepine pharmacotherapies on all-cause mortality of U.S. veterans, including suicide, focusing on practices between 2007 and 2019. The committee applied causal inference methodology and leveraged large VA and Veterans Health Administration (VHA) datasets (e.g., health care, clinical, and administrative data), Centers for Medicare and Medicaid Services data, and the National Death Index to conduct its work. Based on the study findings, the committee concludes the following on all-cause mortality and suicide mortality in veterans who received care from the VHA 2007–2019:

Conclusions 1–2. The committee concludes that there is an increased risk of all-cause mortality among veterans newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy and that there is an increased risk of all-cause mortality among veterans co-prescribed opioid and benzodiazepine pharmacotherapies compared to those co-prescribed non-opioid pain and benzodiazepine pharmacotherapies or to those co-prescribed opioid and alternative non-benzodiazepine pharmacotherapies.

Conclusions 3–4. The committee concludes that there is an increased risk of all-cause mortality among veterans who initiated opioid treatment at higher dosage levels compared to lower levels and that there is an increased risk of all-cause mortality among veterans whose treatment strategy was either slow or fast opioid dosage escalation compared to stable dosage.

Conclusion 5. The committee concludes that there is an increased risk of suicide mortality among veterans newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy.

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Conclusion 6. The committee concludes there is no evidence of a difference in the risk of suicide mortality among veterans newly dispensed opioid pharmacotherapy and currently dispensed benzodiazepine pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy and currently dispensed benzodiazepine pharmacotherapy.

Conclusion 7. The committee concludes that there is some evidence of a higher risk of suicide mortality among veterans co-prescribed opioid and benzodiazepine pharmacotherapy, although the estimate is imprecise at 3 months.

Conclusion 8. Given the lower number of suicide deaths in the eligible population the committee is unable to conduct analyses to address the question of the effect of different opioid dosage treatment strategies on suicide mortality.

Overall, the committee's findings are consistent with concerns regarding the initiation of opioid pharmacotherapy and the concurrent prescribing of benzodiazepine pharmacotherapy. Specifically, concerns about both the prescribing of opioids and the interaction between opioid and benzodiazepine pharmacotherapies appear in VA/Department of Defense clinical practice guidelines in 2010, 2017, and 2022. It is important to note that the committee's interpretation of the results, which occurred in the past, is not intended to influence restriction for any medication nor is it to be viewed as an absolute contraindication for the clinical use of benzodiazepines with opioids.

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Summary

Deaths associated with the co-prescribing of opioid and benzodiazepine pharmacotherapy have raised concerns among health care providers, federal agencies, and the public. The U.S. Congress has expressed concerns particularly about this issue in the veteran population. Veterans are more likely than non-veterans to experience pain, trauma, and mental health conditions from training and combat-related service and be prescribed pharmacotherapies for treatment. The U.S. Congress mandated that the Department of Veterans Affairs (VA) request an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (the National Academies) be assembled to evaluate the effects of prescribed opioid and benzodiazepine pharmacotherapy on all-cause mortality of U.S. veterans, including suicide, focusing on practices between 2007–2019.

Congress's concerns drew attention to two concurrent public health issues: (1) the high prevalence of pain with evidence of less-than-optimal pain management, and (2) high rates of excessive prescription and nonprescription opioid use, misuse, and opioid use disorder (OUD) and related harms, including overdose and mortality. The opioid epidemic in the United States developed over many decades as a result of complex, interconnected factors and therapeutic decisions made by clinicians, health systems, regulators, and professional organizations in an effort to address growing concerns about unrelieved pain. This report does not explore the full history as to how, and why, the opioid epidemic, including concomitant prescribing with benzodiazepine pharmacotherapy, came to be, which has been discussed at length in prior National Academies reports. This report provides a brief summary of the opioid epidemic in the context of the committee's study period of interest (2007–2019) and then focuses on studies (target trial emulations [TTEs]) the committee conducted in response to the statement of task (risks emerging from co-prescribing opioid and benzodiazepine pharmacotherapies).

In particular, the committee evaluated several dimensions of the effect of newly dispensed[1,2] opioid and benzodiazepine pharmacotherapies[3] in the Veterans Health Administration (VHA) on all-cause mortality and suicide.

[1] The committee noted differences in types of pharmacy data measures. Pharmacy data can be categorized into three measures: *prescribed* (prescriber submits a prescription to a pharmacy), *filled* (pharmacy completed the requested prescription), and *dispensed* (individual picks up/is mailed the prescription from the pharmacy). The committee used dispensed pharmacy data in its analyses.

[2] The committee operationalized the term "initiation" in the statement of task as "newly dispensed" pharmacotherapy in analyses. In the committee's studies, "newly dispensed" was defined as pharmacotherapy of interest not previously dispensed (or initiation of pharmacotherapy) to the individual in the last 90 days before the start date.

[3] The committee used the term "pharmacotherapy" throughout the report instead of "medications," "prescriptions," or "treatment," especially when referencing the committee's analyses and results.

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This report examines (1) newly dispensed opioid pharmacotherapy in veterans without and with current benzodiazepine pharmacotherapy, (2) varying levels of the initial baseline dosage and dosage escalation of dispensed opioid pharmacotherapy, and (3) newly dispensed benzodiazepine compared to alternative non-benzodiazepine pharmacotherapy in veterans with consistent opioid pharmacotherapy. The committee's approach, results of the studies, and findings in response to the statement of task are presented next.

CONTEXT OF THE OPIOID EPIDEMIC

Multiple factors contribute to pain as a public health challenge, as outlined in the 2011 Institute of Medicine report *Relieving Pain in America*. These include the large number of people impacted, the disparities in pain prevalence and treatment, differences in the burden on different subgroups, the large indirect and direct economic impact on individuals and society, and the consequential impact of pain treatments. Pain has been linked to higher rates of morbidity, mortality, suicide, disability, and co-occurring psychiatric disorders. Furthermore, treatment of pain is complex, given the heterogeneity of individuals experiencing pain, the need for multimodal approaches to therapy, a lack of understanding of why individuals transition from acute to chronic pain, and the overlapping effects of pain with depression, anxiety, and other psychosocial conditions.

Prescribed Opioid Pharmacotherapy Helps Manage Pain, But Can Contribute to Adverse Outcomes, Including Mortality

In the mid-1990s, the pharmaceutical industry, professional societies, and patient advocacy groups argued that there was an epidemic of untreated pain, and wider use of opioid pharmacotherapy was encouraged. Although opioid pharmacotherapies are prescribed to control pain, they are known to produce feelings of euphoria and sedation, which may contribute to opioid misuse and increased risk of overdose and other drug-related problems. Rapid increases in opioid dosage can inhibit respiration and even lead to death. Higher amounts of opioids are associated with increased risk of OUD,[4] overdose, mortality, and suicide. Increases in opioid prescribing coincided with increasing opioid-related mortality in the United States from the mid-1990s to around 2010. In addition to overdose deaths, studies suggest that the increasing use of prescription opioid pharmacotherapy to manage pain has also correlated with an increased risk of suicide. These trends have been compounded by the increased use of illicit opioids, which are now the main drivers of drug overdose deaths.

The co-prescribing of benzodiazepine and opioid pharmacotherapies has raised additional concerns. Whereas opioid pharmacotherapy is primarily prescribed for pain, benzodiazepine pharmacotherapy is typically prescribed for anxiety, panic disorders, insomnia, and seizures. The combination of opioid and benzodiazepine pharmacotherapies is known to have potential adverse respiratory effects, as the sedating effects of benzodiazepines can further suppress breathing in individuals experiencing opioid-induced respiratory depression. Data on causes of death in overdose fatalities published by the National Institute of Drug Abuse indicate that the percent of drug overdose deaths with concomitant benzodiazepine pharmacotherapy rose dramatically in the initial period of the opioid epidemic from 1999 to 2010 and has been falling slowly since. Although several studies examine the risk of concurrent opioid and benzodiazepine pharmacotherapy, the level of risk and the relationship of these deaths to the concomitant prescribing of opioid and benzodiazepine pharmacotherapies compared to other pharmacotherapies (active comparator) have never been studied.

Pain and Opioid Prescribing in the Veteran Population

Studies have demonstrated that a higher percentage of veterans experience pain compared to non-veterans, which is attributable to the physical demands of military service, including training and combat-related injuries.

[4] The *Diagnostic and Statistical Manual of Mental Disorders—5* defines opioid use disorder (OUD) as "a problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the [11 diagnostic criteria], occurring within a 12-month period."

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Veterans are also more likely to experience chronic health conditions, psychological distress, and a higher incidence of suicide than non-veterans (civilians). As a result, veterans are more likely than the general population to need care for chronic pain and other conditions.

About 9 million U.S. veterans receive health care services each year from the VHA, the largest integrated health care network in the country. VHA veterans (those who obtain care through the VHA) differ from non-VHA veterans (those who obtain health care from non-VHA health care providers), with a statistically significant higher prevalence of both physical and mental health conditions, such as posttraumatic stress disorder, anxiety, and depression even after adjusting for demographic characteristics. In addition, VHA veterans were more likely to report chronic pain than non-VHA veterans (45.2 percent versus 26.8 percent). In addition, among VHA veterans, the rate of OUD was 7 times higher than that of non-VHA veterans.

Similar to national trends, the prevalence of receiving an opioid prescription[5] increased over time within the VHA, from about 19 percent of veterans in 2004 to 33 percent in 2012. Overall, opioid prescribing in the VHA declined thereafter. Between 2004–2009, 27 percent of VHA veterans who received opioid pharmacotherapy also received benzodiazepine pharmacotherapy. Of the drug overdose deaths observed during that period, nearly half occurred in VHA veterans concurrently prescribed benzodiazepines and opioid pharmacotherapies. Another study compared the risk of adverse outcomes (accidents and injuries, non-fatal overdose events, and death) in VHA veterans who received long-term opioid prescription[6] ($N = 924,656$) to VHA veterans who received concomitant opioid and benzodiazepine pharmacotherapies ($N = 110,305$). VHA veterans with concomitant pharmacotherapies had a 36 percent higher risk of an adverse outcome (e.g., opioid-related overdose, self-inflicted injury, all-cause mortality).

CLINICAL GUIDELINES, POLICIES, AND LEGISLATION RELEVANT TO UNDERSTANDING THE CONTEXT OF THE OPIOID EPIDEMIC

In response to the adverse outcomes associated with the trends in prescribed opioid pharmacotherapy, several VHA clinical guidelines and policies addressing the opioid epidemic have been issued, including during the committee's study period (2007–2019).[7] The VHA set forth guidelines in 2003 to support clinical decision making around pain management and opioid treatment. VHA clinical guidelines continued to evolve through the years (2010, 2017, 2022) along with the agency-wide 2013 VHA Opioid Safety Initiative, which, among many efforts, increased education and monitoring and promoted effective prescribing. These efforts were complemented by other federal agency efforts, such as clinical guidelines from the Centers for Disease Control and Prevention (CDC) in 2016 and 2022 and Department of Health and Human Services in 2019. Federal legislation, such as the Veterans Access, Choice and Accountability Act (2014), the Comprehensive Addiction and Recovery Act (2016), and the VA Mission Act (2018), was passed during the study time frame, intended to help support veterans or reduce harms related to the opioid overdose crisis.

[5] Opioid prescription in the cited study was based on the receipt of an opioid prescription, using VHA outpatient prescription fill.

[6] Individuals receiving long-term opioid prescription were categorized as "chronic" or "high-risk." "Chronic" was defined as receiving a 90-day or greater opioid prescription, with less than a 30-day gap in supply and within a 180-day period. "High-risk" was defined as those with ≥1 substance use disorder diagnosis (excluding tobacco) and/or an average opioid dose of ≥100 morphine milligram equivalent (MME)/day. Concomitant prescribing was defined as the receipt of both opioid and benzodiazepine prescriptions, with >7 days of overlap of both prescriptions.

[7] In 1999, the VHA followed the American Pain Society recommendations, integrating the Pain as the 5th Vital Sign Initiative into the VHA National Pain Management Strategy, whereby routine screening, a published comprehensive pain assessment and management toolkit, and educational campaigns were launched.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

CONGRESSIONAL MANDATE TO ADDRESS CONCERNS ABOUT PRESCRIBING OPIOIDS AND BENZODIAZEPINES IN THE VETERAN POPULATION

In 2019, through the Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019,[8] Congress mandated that the VA request an ad hoc committee of the National Academies be assembled "to evaluate the effects of opioids and benzodiazepine on all-cause mortality of veterans, including suicide, regardless of whether information relating to such deaths has been reported by the Centers for Disease Control and Prevention" (see Box S-1). The legislation stated that the request was "a revised study design to fulfill the goals of the 2019 study design of the National Academies." The study designs developed by this current committee were based on the study designs, or target trial protocols, presented in the congressionally mandated 2019 National Academies report *An Approach to Evaluate the Effects of Concomitant Prescribing Opioids on Veteran Deaths and Suicides*.

The 2019 report applied the TTE framework in its proposed target trial protocols to emulate, using observational data, randomized controlled trials (RCTs). The 2019 report proposed two study designs ("opioid treatment initiation" and "opioid tapering") to address the effect of prescribed opioid pharmacotherapy on all-cause mortality and suicide mortality. The 2019 report outlined specific study components to consider: eligibility criteria, treatment strategies, treatment assignment, start and end of follow-up, outcomes, causal contrasts, and statistical approach.

STUDY CHARGE AND APPROACH

In response to the congressional mandate, the National Academies convened a 13-member committee with expertise in pain, mental health, neurology, addiction, epidemiology, pharmacoepidemiology, statistics, VHA health data systems, and VHA and non-VHA care of mental health and pain in veterans. This committee leveraged use of the TTE framework mentioned in the 2019 National Academies report, as well as refined the study designs to respond to this statement of task. The committee developed causal research questions to align with the statement of task, identified comparator groups to align with "alternative non-opioid pain treatments" and "alternative treatments for anxiety and other indications for benzodiazepines," and refined the protocols to use available observational electronic health record (EHR) data, data from VHA administrative and clinical databases, and mortality data from the National Death Index. Considering the available data, the committee operationalized the statement of task into the following causal questions, which are then addressed in three distinct studies:

BOX S-1
Statement of Task

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will evaluate the effects of opioid and benzodiazepine use on all-cause mortality of U.S. veterans, including suicide, regardless of whether information relating to such deaths has been reported to the U.S. Centers for Disease Control and Prevention. Specifically, the committee will quantify the effects of opioid and benzodiazepine prescribing on the risk of death among veterans who received care from the Department of Veterans Affairs (VA) between 2007 and 2019. In their analysis, the committee will focus on

(a) the effect of opioid prescribing for pain, relative to alternative non-opioid pain treatments,

(b) the effects of higher doses relative to lower doses of opioids,

(c) the effect of co-prescribing a benzodiazepine among patients already receiving opioids, relative to alternative treatments for anxiety and other indications for benzodiazepines, and

(d) the effect of initiating opioids among patients already taking benzodiazepines.

[8] Public Law 116-171 Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019, 116th Congress, October 17, 2020. See also appendix C for the full language of Section 204 of the Act, specific to this study.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

- Among veterans receiving care in the VHA who were not consistently[9] dispensed pain pharmacotherapy between 2007–2019, what is the effect of newly dispensed[10] opioid versus non-opioid pain pharmacotherapy on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) among those without and with current use of benzodiazepine pharmacotherapy within a 12-month follow-up period? (Study 1)
- Among veterans receiving care in the VHA who were newly dispensed full agonist[11] opioid pharmacotherapy between 2007–2019, what is the effect of different initial opioid dosage and escalation strategies on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) within a 12-month follow-up period? (Study 2)
- Among veterans receiving care in the VHA who were consistently[12] dispensed opioid pharmacotherapy between 2007–2019, what is the effect of newly dispensed benzodiazepine versus alternative non-benzodiazepine pharmacotherapy for anxiety and other common indications for benzodiazepines on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) within a 3-month follow-up period? (Study 3)

For all studies, the committee did not include "chronic pain" in the causal question or as a covariate for several reasons. There are multiple factors that limit the reliability of pain-relevant diagnosis codes and their utility in observational research. First and foremost, there are challenges in its measurement and capture, such as potential underreporting of the large variety of diagnoses associated with chronic pain diagnoses and the underlying painful conditions. Preliminary analysis indicated that 37.7 percent of eligible participants who were dispensed an opioid pharmacotherapy did not have a diagnosis code related to chronic pain. Accurate diagnosis can be complicated and emerge over time as a comprehensive assessment proceeds (e.g., diagnosis of low back pain). Further, providers may vary in the reporting of pain-relevant diagnostic codes, which may further contribute to unreliability. Additionally, individuals with chronic pain report multiple sites of pain and multiple pain conditions, further complicating the use of diagnosis codes to characterize the pain experience and to reliably associate diagnosis with treatment decisions. Yet, opioid pharmacotherapy is used for a wide variety of pain conditions. Given the challenges in capturing pain and chronic pain, the committee assumed that most individuals who were dispensed an opioid prescription received it to manage pain (via opioids' known analgesic effects). The indication of pain was used to choose the non-opioid pharmacotherapies included in study 1, to control for confounding by indication. Finally, the term is not reflected in the statement of task.

The committee noted that there are several aspects of opioid prescribing that were not stated in the statement of task and not reflected in the committee's analyses. The committee did not implement the opioid tapering target trial protocol suggested in the 2019 report, considering the following factors in its decision. First, the current statement of task did not direct the committee to examine the effect of opioid tapering on mortality. Second, the committee was aware of studies based on the 2019 report protocol that had been or were being completed and commissioned a review of these and other relevant studies conducted since the 2019 report (see Appendix E). Based on the review, the committee determined that the risk of immortal time and selection biases is high and substantially limits the extent to which retrospective observational studies can infer causality between opioid tapering and mortality. Of note, Dr. Erin Krebs and her colleagues applied the 2019 protocol in an unpublished study (see Appendix F) included in the review. The committee noted, and based on the presentation by the author, that the study's findings and conclusions were highly sensitive to different study design elements, statistical modeling, and measurement strategies. In addition, the treatment assignment was based on pharmacy records and as such

[9] Not dispensed any qualifying opioid or non-opioid pain pharmacotherapy in the 90-day pre-index period.

[10] The committee operationalized the term "initiation" in the statement of task as "newly dispensed" pharmacotherapy in analyses. In the committee's studies, "newly dispensed" was defined as pharmacotherapy of interest not previously dispensed (or initiation of pharmacotherapy) to the individual in the last 90 days before the start date.

[11] There are two types of opioids: full agonist and partial opioid agonist. Full opioid agonists fully activate the mu receptors in the brain, enabling the opioid to have "full" effect, such as codeine, oxycodone, and fentanyl. Partial opioid agonists also activate mu receptors in the brain but to a lesser degree, such as butorphanol or tapentadol.

[12] The committee defined as three or more dispensed opioids at least 21 days apart within a 180-day period for at least 84-day supply or two dispensed opioids of 90-day supply within 180 days.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

may not accurately reflect whether a tapering was intended or actually took place. Based on these observations, not available at the time of the 2019 report, the committee concluded that additional efforts to implement such a study is unlikely to yield more definitive results and, for these reasons, the committee chose not to implement the tapering trial suggested in the 2019 report. The committee focused the main report to reflect findings from the analyses addressing the statement of task.

The statement of task also did not direct the committee to compare mortality of veterans prescribed opioids and benzodiazepines in the VHA to veterans prescribed opioids and benzodiazepines in other health care systems. Thus, comparing VHA and non-VHA providers was not part of the committee's work. In addition, the committee noted that the focus of the statement of task is to examine the risk, not the benefits, of prescribing opioid and benzodiazepine pharmacotherapies. Beyond non-opioid pain pharmacotherapy, the committee did not investigate the impact of other alternative treatments for pain, such as non-pharmacologic approaches as this was outside the scope of the statement of task.

Furthermore, the committee noted that the statement of task specifically mandated the study period (2007–2019) to understand the implications of opioid treatment on mortality in veterans. Therefore, the findings of this report are not intended to be applicable to current practices or behaviors, including those of the VHA. In addition, these retrospective studies are inherently forensic, reflecting the effect of care that occurred in the past rather than being indicative of the mortality risks of current practices, particularly given the ongoing changes in opioid prescribing practices, the policy landscape, mental health care, and the nature of the opioid overdose epidemic in the intervening years. As reflected in the statement of task and expert perspectives, many unanswered questions remain about the causal effects of past opioid prescribing practices on mortality, especially in light of ecologic data indicating that U.S. opioid- and benzodiazepine-pharmacotherapy–related mortality has continued to climb in recent years.

In sum, the committee sought to address the statement of task in the least biased and most internally valid way, which calls on the committee to utilize best practices and recent advances in the modern causal inference literature, including TTE techniques. The committee applied this strategy to estimate causal effects of several key opioid and benzodiazepine pharmacotherapy prescribing decision points—to initiate opioid pharmacotherapy, increase opioid dosages over time, and co-prescribe opioid and benzodiazepine pharmacotherapies. The committee was explicit in the causal objective, which can reduce ambiguity in the scientific question and errors in data analysis and clarify assumptions required for causal inference. The committee adhered to best practices from the modern causal inference literature, including (1) designing the observational analysis to emulate a target trial and (2) selecting confounding adjustment variables using expert knowledge and clear articulation of the causal structure of the study question.

ANALYTIC APPROACH

In line with the 2019 report, the current committee employed the TTE framework. The committee considered two designs: experimental or RCTs and non-experimental, or observational, studies. RCTs are experimental studies in which participants are randomly assigned, or randomized, to treatment strategies. Randomization minimizes confounding and assures balance across treatment groups. While RCTs[13] are the gold standard for assessing the causal effects of medical treatments, barriers to implementation include prohibitively high costs and time demands, ethical dilemmas around the random allocation to medications with potentially negative side effects, potential for mistreatment of historically vulnerable populations, and potentially small sample sizes in the case of rare medical disorders or outcomes. In the last 3 decades, notable progress has been made in estimating the causal effects of medical treatment beyond the confines of RCTs, such as through observational study designs. In observational studies, the investigator does not randomize individuals into different treatment strategies, but rather observes to examine outcomes in each treatment strategy. With no randomization, there is a risk of confounding. The committee recognized other approaches to adjust for confounding (e.g., instrumental variables, regression discontinuity)

[13] A key advantage of RCTs is protocol-based outcomes ascertainment, which is a limitation with observational studies. This ascertainment can help reduce bias due to misclassification of outcomes, exposure, and confounders.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

in observational data, but the committee leveraged the TTE framework. The TTE framework is an advance in the modern causal inference literature to approach designing an observational study to mimic a hypothetical randomized experiment, or target trial. The TTE framework helps to ensure the observational study compares realistic clinical treatment strategies, avoids biases related to mishandling time zero, and improves upon conventional methods to address baseline and time-varying confounding. However, the impact of unmeasured confounding and immortal time bias still remains a risk in observational studies, unlike RCTs; sensitivity analyses and alternative assumptions about confounding should be taken into consideration.

Study Population, Data Sources, and Statistical Approach

The study population was defined as veterans receiving care in the VHA from January 1, 2007, to December 31, 2019.[14] Data were drawn from national VHA data files and linked to the VA Corporate Data Warehouse, U.S. Veterans Eligibility Trends and Statistics, and Centers for Medicare & Medicaid Services (CMS) Medicare Parts A, B, C, and D data. The CMS Medicare data were used to supplement VHA data. The National Academies Institutional Review Board approved the study.

Each of the three studies was designed as a comparison between the exposure of interest (individuals receiving opioid pharmacotherapy, for example) to another exposure (individuals receiving non-opioid pain pharmacotherapy, for example). In identifying pharmacotherapy for either the treatment or comparator groups in each study, the committee relied on clinical expertise, Food and Drug Administration-approved indications, VHA drug classifications, and a review of existing literature. Pharmacotherapy data were drawn from either VHA EHR or Medicare Part D pharmacy claims data; medications selected for analyses were not limited to those on the CMS or VHA formularies. Use of an active comparator reduces the risk of confounding by the indication for therapy. However, that risk still exists, as different drugs are used differently and have different safety concerns. A perfect active comparator to opioid pharmacotherapy or benzodiazepine pharmacotherapy does not exist. However, the comparator groups selected are less biased than including individuals who were not an active comparator. Per the statement of task, all-cause mortality (primary outcome) and suicide mortality (secondary outcome) were the study outcomes.

The causal effects on the study outcomes were estimated using both per protocol effect and intent-to-treat effect (ITT) methodologies. The per protocol approach estimated the effect of being newly dispensed and continuously adhering[15] to the treatment of interest during follow-up. The ITT approach characterized the effect of newly dispensed treatments from initiation to the end of the study, irrespective of whether an individual changed their treatment during follow-up (e.g., cross-over to another exposure group or treatment discontinuation). Unadjusted and adjusted pooled logistic regressions (studies 1 and 3) and the parametric G-formula (study 2) were the statistical methods, hazard ratios (study 1 and 3) and risk ratio (study 2) were estimated, and statistical inference is represented by the calculated confidence intervals. All analyses were conducted using SAS 9.4 and SAS Enterprise Guide. To strengthen causal inferences, the committee adjusted for many potential covariates, which included demographic characteristics (e.g., age, sex, race/ethnicity, marital status, disability status), supplemental insurance to VHA coverage (i.e., Medicare, TRICARE, or private insurance), housing security (e.g., history of homelessness status), physical and mental health conditions/disorders (e.g., acute painful injury, anxiety, chronic obstructive pulmonary disease, cardiovascular disease, substance use disorders, diabetes), military status (e.g., service era, military branch, combat service), body mass index, health care utilization in prior year (e.g., VHA outpatient visits, inpatient hospital admissions, nursing home stay), VHA facility-level characteristic (e.g., urbanicity), and specific pharmacotherapies that the committee considered as potential confounders. The committee considered all potential confounders, the validity of measures of covariates in the available datasets, and then sought parsimony in the final models to minimize imprecision introduced by including variables that were not confounders.

[14] Latest possible index date was December 31, 2018, in studies 1 and 2 and October 1, 2019, in study 3.

[15] Adherence to treatment of interest in the context of this report indicates that individuals continuously followed the treatment protocol of the specific study.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

FINDINGS

The results and findings of the three studies are presented next. Each of the studies examined all-cause mortality and suicide mortality and focused on different aspects of opioid prescribing. Study 1 evaluates veterans who are newly dispensed opioid pharmacotherapy to those veterans newly dispensed non-opioid pain pharmacotherapy, without and with currently dispensed benzodiazepine pharmacotherapy. Study 2 evaluates two opioid prescribing strategies: varying initial dosages of opioid pharmacotherapy and varying opioid dosage escalation. Study 3 compares veterans who are newly dispensed benzodiazepine pharmacotherapy to those newly dispensed alternative non-benzodiazepine pharmacotherapy, among veterans who are consistently dispensed opioid pharmacotherapy.

Study 1: The Effect of Newly Dispensed Opioid Pharmacotherapy on All-Cause Mortality and Suicide Mortality, Among Veterans Without and With Currently Dispensed Benzodiazepine Pharmacotherapy

The first study addresses parts (a) and (d) of the statement of task. Specifically, the study focused on (a) the effect of opioid prescribing for pain compared to alternative non-opioid pain treatments, and (d) the effect of initiating opioids in individuals who are already taking benzodiazepines. The available data were stratified into two populations, based on current pharmacotherapy status: without[16] (study 1a) and with[17] (study 1b) current benzodiazepine pharmacotherapy.

Study 1a: The Effect of Newly Dispensed Opioid Pharmacotherapy on All-Cause Mortality and Suicide Mortality Among Veterans Without Current Benzodiazepine Pharmacotherapy

This study had 5,636,207 unique veterans, of whom 71 percent were newly dispensed non-opioid pain pharmacotherapy and 29 percent newly dispensed opioid pharmacotherapy. Study results are included in Table S-1.

Finding 1a-1. Among veterans without current benzodiazepine pharmacotherapy, the 12-month risk of all-cause mortality was 10,273 deaths per 100,000 person-years for those newly dispensed opioid pharmacotherapy and 6,473 deaths per 100,000 person-years for those newly dispensed non-opioid pain pharmacotherapy (aHR:[18] 1.61; 95% CI: 1.59–1.63).

TABLE S-1 Study 1a Results. The Effect of Newly Dispensed Opioid Pharmacotherapy† on All-Cause Mortality, Including Suicide Mortality, Among VHA Veterans Without Current Benzodiazepine Pharmacotherapy†† (2007–2019; *N* = 5,636,207)

	Adjusted Mortality Rate *Deaths per 100,000 person-years*		
	Newly Dispensed		
Outcome	**Opioid Pharmacotherapy** *Treatment*	**Non-Opioid Pain Pharmacotherapy** *Comparator*	**Adjusted Hazard ratio (95% CI[1])**
All-cause mortality	10,273	6,473	1.61 (1.59–1.63)
Suicide mortality	112	95	1.19 (1.07–1.32)

[1] Confidence Intervals

†Defined as first occurrence of ≥7-day supply of a newly dispensed opioid or non-opioid pain pharmacotherapy. "Newly dispensed" is defined as having no exposure of opioid or non-opioid pain pharmacotherapy 90 days prior to the first occurrence.

††Without current benzodiazepine pharmacotherapy is defined as receiving <5 tablets of benzodiazepines within 90 days prior to the first occurence.

NOTE: No cells are reported representing 10 or fewer veterans; results are per protocol effect.

[16] Defined as <5 tablets of benzodiazepine pharmacotherapy within 90 days pre-index period.

[17] Defined as ≥ 5 tablets of benzodiazepine pharmacotherapy within 90 days pre-index period.

[18] aHR: adjusted hazard ratio.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Finding 1a-2. Among veterans without current benzodiazepine pharmacotherapy, the 12-month risk for suicide mortality was 112 deaths per 100,000 person-years for those newly dispensed opioid pharmacotherapy and 95 deaths per 100,000 person-years for those newly dispensed non-opioid pain pharmacotherapy (aHR: 1.19; 95% CI 1.07–1.32).

Study 1b: The Effect of Newly Dispensed Opioid Pharmacotherapy on All-Cause Mortality and Suicide Mortality Among Veterans With Current Benzodiazepine Pharmacotherapy

This study had 319,990 unique veterans with current benzodiazepine pharmacotherapy, of whom 65 percent were newly dispensed non-opioid pain pharmacotherapy and 35 percent newly dispensed opioid pharmacotherapy. Study 1b results are included in Table S-2.

Finding 1b-1. Among veterans with current benzodiazepine pharmacotherapy, the 12-month risk for all-cause mortality was 11,877 deaths per 100,000 person-years for those newly dispensed opioid pharmacotherapy and 7,441 deaths per 100,000 person-years for those newly dispensed non-opioid pain pharmacotherapy (aHR: 1.59; 95% CI: 1.53–1.65).

Finding 1b-2. Among veterans with current benzodiazepine pharmacotherapy, the 12-month risk for suicide mortality was 246 deaths per 100,000 person-years for those newly dispensed opioid pharmacotherapy and 238 deaths per 100,000 person-years for those newly dispensed non-opioid pain pharmacotherapy (aHR: 1.03; 95% CI: 0.81–1.31).

Study 2: The Effect of Initial Opioid Dosage and Opioid Dosage Escalation Strategies on All-Cause Mortality and Suicide Mortality

The second study addresses part (b) of the statement of task, to examine the effects of higher doses relative to lower doses of opioids. The study emulated two trials: one examined the effect of different initial opioid dosage and the other, the effect of different opioid dosage escalation strategies.

Study 2a: The Effect of Initial Opioid Dosage Strategies on All-Cause Mortality and Suicide Mortality

Study 2a results are included in Table S-3.

TABLE S-2 Study 1b Results. The Effect of Newly Dispensed Opioid Pharmacotherapy† on All-Cause Mortality and Suicide Mortality Among VHA Veterans with Current Benzodiazepine Pharmacotherapy†† (2007–2019; *N* = 319,990)

	Adjusted Mortality Rate *Deaths per 100,000 person-years*		
	Newly Dispensed		
Outcome	**Opioid Pharmacotherapy** *Treatment*	**Non-Opioid Pain Pharmacotherapy** *Comparator*	**Adjusted Hazard Ratio (95% CI[1])**
All-cause mortality	11,877	7,441	1.59 (1.53–1.65)
Suicide mortality	246	238	1.03 (0.81–1.31)

[1] Confidence Intervals

†Defined as first occurrence of ≥7-day supply of a newly dispensed opioid or non-opioid pain pharmacotherapy. "Newly" is defined as having no exposure of opioid or non-opioid pain pharmacotherapy 90 days prior to the first occurrence.

††With current benzodiazepine pharmacotherapy is defined as receiving ≥5 tablets of benzodiazepine pharmacotherapy within 90 day prior to the first occurrence.

NOTE: No cells are reported representing 10 or fewer veterans; results are per protocol effect.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE S-3 Study 2a Results. Among VHA Veterans Newly Dispensed Full Agonist Opioid Pharmacotherapy, the Estimated Risk of All-Cause Mortality and Risk Ratio by Initial Opioid Dosage (2007–2019; *N* = 5,639,108)

Initial Opioid Dosage Strategy[a] (MME/Day)	**Risk Estimate (%)**	**Bootstrap SE**[1]	**95% CI**[b]	**Risk Ratio**	**95% CI**[b]
Low (>0 to ≤20)	3.95	0.16	3.69–4.29	1.00	(Ref)
Medium (>20 to ≤40)	4.89	0.19	4.55–5.33	1.24	1.20–1.28
High (>40 to ≤50)	5.80	0.19	5.44–6.24	1.47	1.44–1.50

[1] SE: standard error.

[a] Initial dosage strategy is calculated as the average morphine milligram equivalent (MME)/day during the index month. The MME is a measure of the intensity of opioid exposure; it standardizes opioid prescriptions considering differences in the potency, quantity, and strength of different types of dispensed opioids. The committee calculated it using CDC conversions.

[b] Confidence intervals (CI) were calculated using the percentile method from 400 bootstrap samples.

NOTE: In conducting the analysis, no cells are reported representing 10 or fewer veterans.

Finding 2a-1. Among veterans with newly dispensed opioid pharmacotherapy, the 12-month risk of all-cause mortality in each of the initial opioid dosage strategy was 3.95 percent for low, 4.89 percent for medium, and 5.80 percent for high. ($RR^{19}_{\text{medium vs low}}$: :1.24; 95% CI: 1.20–1.28] and $RR_{\text{high vs low:}}$ 1.47: 95% CI: 1.44–1.50]).

Finding 2a-2. Among veterans with newly dispensed opioid pharmacotherapy, the committee is unable to draw conclusions about the effect of those who received a high or medium initial daily opioid dosage level, compared to veterans with a low initial daily opioid dosage level on suicide mortality within 12-months of follow-up, due to the lower number of suicide deaths in the eligible population.

Study 2b: The Effect of Escalating Opioid Dosage Strategies on All-Cause Mortality and Suicide Mortality

Study 2b results are included in Table S-4.

Finding 2b-1. Among veterans with newly dispensed opioid pharmacotherapy, the 12-month risk of all-cause mortality in each of the dosage escalation strategies was 2.70 percent for stable, 4.56 percent for slow, and 4.69 percent for fast over the first six months. ($RR_{\text{slow vs stable}}$: 1.69; 95% CI: 1.53–1.80] and $RR_{\text{fast vs stable}}$: 1.74; 95% CI: 1.57–1.95]).

Finding 2b-2. The committee is unable to draw conclusions about the effect of escalating dosages of opioid pharmacotherapy on suicide mortality within 12 months of follow-up, due to the lower number of suicide deaths in the eligible population.

[19] RR: risk ratio.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE S-4 Study 2b Results. Among VHA Veterans Newly Dispensed Full Agonist Opioid Pharmacotherapy, the Estimated Risk Of All-Cause Mortality and Risk Ratio by Dosage Escalation Strategies (2007–2019; *N* = 5,639,108)

Dosage Opioid Escalation Strategy[a] (Average MME/day change in 6 months)	**Risk Estimate (%)**	**Bootstrap SE**[1]	**95% CI**[b]	**Risk Ratio**	**95% CI**[b]
Stable (0 to <5)	2.70	0.18	2.34–3.08	1.00	(Ref)
Slow (≥5 to <10)	4.56	0.17	4.27–4.92	1.69	1.53–1.89
Fast (≥10 to <20)	4.69	0.17	4.39–5.06	1.74	1.57–1.94

[1] SE: standard error.

[a] Dosage escalation strategy is calculated as the average morphine milligram equivalent (MME)/day change in 6 months. The MME is ideal to measure the intensity of opioid exposure, as it standardizes opioid prescriptions considering differences in the potency, quantity, and strength of different types of dispensed opioids. The committee calculated it using CDC conversions.

[b] Confidence intervals were calculated using the percentile method from 400 bootstrap samples.

NOTE: In conducting the analysis, no cells are reported representing 10 or fewer veterans.

Study 3: The Effect of Benzodiazepine Pharmacotherapy Co-Prescribing on All-Cause Mortality and Suicide Mortality Among VHA Veterans with Consistently Dispensed Opioid Pharmacotherapy[20]

The third study addresses the objective outlined in part (c) of the statement of task. Specifically, the study focused on the effect of newly dispensed benzodiazepine pharmacotherapy in VHA veterans consistently dispensed opioid pharmacotherapy compared to VHA veterans who were consistently dispensed alternative non-benzodiazepine pharmacotherapy.

There were 637,793[21] unique veterans who were consistently dispensed opioid pharmacotherapy and eligible for inclusion. About 19.4 percent of the sample were newly dispensed benzodiazepine pharmacotherapy, and about 88.6 percent were newly dispensed alternative non-benzodiazepine pharmacotherapy. Study 3 results are included in Table S-5.

Finding 3-1. Among veterans consistently dispensed opioid pharmacotherapy, the 3-month risk for all-cause mortality was 7,493 deaths per 100,000 person-years for those newly dispensed benzodiazepine pharmacotherapy and 4,392 per 100,000 person-years for those newly dispensed alternative non-benzodiazepine pharmacotherapy (aHR: 1.71; 95% CI: 1.60–1.82).[22]

Finding 3-2. Among veterans consistently dispensed opioid pharmacotherapy, the 3-month risk for suicide mortality was 117 deaths per 100,000 person-years for those newly dispensed benzodiazepine pharmacotherapy and 83 deaths per 100,000 person-years for those newly dispensed alternative non-benzodiazepine pharmacotherapy (aHR: 1.42; 95% CI: 0.87–2.31).[23]

CONCLUSIONS

The committee, through three studies, evaluated the effect of dispensed opioid and benzodiazepine pharmacotherapies on all-cause mortality and suicide mortality. The studies focused on effects of newly dispensed opioid or benzodiazepine pharmacotherapy, the co-prescribing of opioids and benzodiazepine pharmacotherapy, and different

[20] Consistently dispensed opioid pharmacotherapy is also known as "long-term opioid treatment."

[21] During the study period (2007–2019), a veteran could enter the study more than one time and contribute more than one episode. Thus, the number of veterans in the benzodiazepine group (*N* = 123,684) and alternative non-benzodiazepine comparator (*N* = 565,481) will not sum to 637,793.

[22] Alternative non-benzodiazepine pharmacotherapy can be used to treat conditions treated by benzodiazepines, such as anxiety.

[23] Alternative non-benzodiazepine pharmacotherapies can be used to treat conditions treated by benzodiazepines, such as anxiety.

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TABLE S-5 Study 3. The Effect of Benzodiazepine Pharmacotherapy Co-Prescribing† on All-Cause Mortality, Including Suicide Mortality, Among VHA Veterans with Consistently Dispensed Opioid Pharmacotherapy†† (2007–2019; *N* = 637,793)

	Adjusted Mortality Rate *Deaths per 100,000 person-years*		
	Newly Dispensed		
Outcome	**Benzodiazepine Pharmacotherapy** *Treatment* (*N* = 123,684)	**Alternative Non-Benzodiazepine Pharmacotherapy**††† *Comparator* (*N* = 565,481)	Adjusted Hazard Ratio (95% CI)
All-cause mortality (*N* = 16,193)	7,493	4,392	1.71 (1.60–1.82)
Suicide mortality (*N* = 303)	117	83	1.42 (0.87–2.31)

†≥1 tablet of benzodiazepine pharmacotherapy.

†† Consistently dispensed opioid pharmacotherapy: Dispensed ≥3 opioid prescriptions within a 180-day window with (1) ≥two 21-day gaps between prescriptions and (2) an 84+ day supply within the 180-day window OR two 90-day opioid prescriptions within 180-day window.

†††Alternative non-benzodiazepine pharmacotherapy includes pharmacotherapies used to manage anxiety or other common indications for benzodiazepine pharmacotherapy.

NOTE: In conducting the analysis, no cells are reported representing 10 or fewer veterans.

opioid dosage treatment strategies. The committee employed the TTE framework to reduce biases, such as due to immortal time, and confounding. In addition, the committee leveraged the large observational datasets (e.g., health care, clinical, and administrative data) available within the VA and VHA, supplemented by CMS data, and the National Death Index for mortality data. Based on the study findings, the committee concludes the following in veterans who received care from the VHA between 2007–2019:

Conclusion 1. The committee concludes that there is an increased risk of all-cause mortality among veterans newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy.

Conclusion 2. The committee concludes that there is an increased risk of all-cause mortality among veterans co-prescribed opioid and benzodiazepine pharmacotherapies compared to those co-prescribed non-opioid pain and benzodiazepine pharmacotherapies or to those co-prescribed opioid and alternative non-benzodiazepine pharmacotherapies.

Conclusion 3. The committee concludes that there is an increased risk of all-cause mortality among veterans who initiated opioid treatment at higher dosage levels compared to lower levels.

Conclusion 4. The committee concludes that there is an increased risk of all-cause mortality among veterans whose treatment strategy was either slow or fast opioid dosage escalation compared to stable dosage.

Regarding suicide mortality, the results were less conclusive. Based on the study findings, the committee concludes the following in veterans who received care from the VHA between 2007–2019:

Conclusion 5. The committee concludes that there is an increased risk of suicide mortality among veterans newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy.

Conclusion 6. The committee concludes there is no evidence of a difference in the risk of suicide mortality among veterans newly dispensed opioid pharmacotherapy and currently dispensed benzodiazepine pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy and currently dispensed benzodiazepine pharmacotherapy.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Conclusion 7. The committee concludes that there is some evidence of a higher risk of suicide mortality among veterans co-prescribed opioid and benzodiazepine pharmacotherapy, although the estimate is imprecise at 3 months.

Conclusion 8. Given the lower number of suicide deaths in the eligible population the committee is unable to conduct analyses to address the question of the effect of different opioid dosage treatment strategies on suicide mortality.

Overall, the committee's findings are consistent with concerns regarding the initiation of opioid pharmacotherapy and concurrent prescribing of benzodiazepine pharmacotherapy. Specifically, concerns about both the prescribing of opioid pharmacotherapy and the interaction between the two pharmacotherapies first appeared in the VA/Department of Defense clinical practice guidelines in 2010 and continued to be raised in the 2017 and 2022 guidelines. In addition, the committee's findings are based on data on veterans treated by the VHA, as specified in the statement of task; the analysis does not compare the experiences of veterans and prescribing practices of non-VHA providers in other health care systems (which is not reflected in the statement of task). It is important to note that the committee's interpretation of the results, which occurred in the past, is not intended to influence restriction for any medication nor is it to be viewed as an absolute contraindication for the clinical use of benzodiazepines with opioids.

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1

Introduction

OVERVIEW

Deaths associated with the co-prescribing of opioid and benzodiazepine pharmacotherapy have raised concerns among health care providers, federal agencies, and the public. Concerns about the outcomes associated with prescribing patterns of opioid pharmacotherapy, benzodiazepine pharmacotherapy, and opioid-benzodiazepine co-prescribing persist, given the high prevalence of pain with evidence of less-than-optimal management and high rates of excessive prescription and nonprescription opioid use, misuse, and opioid use disorder (OUD) and related harms, including overdose and mortality. This chapter provides an overview of the trends in prescribing of opioid, benzodiazepine, and concomitant opioid and benzodiazepine pharmacotherapies in the context of the opioid epidemic and the need for pain management among the veteran population. This chapter also describes the committee's approach in addressing the statement of task. In Chapter 2, the committee describes the clinical practice guidelines, policies, and federal legislations relevant to understanding the context of the opioid epidemic, which developed over several decades as a result of complex, interconnected factors and therapeutic decisions made by clinicians, health systems, regulators, and professional organizations to address growing concerns about unrelieved pain (Jones et al., 2018). This report does not explore the full history as to how, and why, the opioid epidemic came to be, as it has been discussed at length in prior National Academies of Sciences, Engineering, and Medicine (National Academies) reports (NASEM, 2017, 2020; IOM, 2011). This chapter provides a brief summary of the opioid epidemic in the context of the committee's study period (2007–2019).

CONTEXT OF THE OPIOID EPIDEMIC

Pain Is, and Continues to Be, a Public Health Challenge

Multiple factors contribute to pain as an ongoing public challenge, as outlined in the 2011 Institute of Medicine (IOM) report *Relieving Pain in America*, specifically the large number of people impacted, disparities in pain prevalence and treatment, differences in the burden on different subgroups, large indirect and direct economic impact on individuals and society, and consequential impact of pain treatments. Pain, defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020), has been linked to higher rates of morbidity, mortality, suicide, and disability (IOM, 2011). Furthermore, there is a clear association between pain and mental health. Pain, particularly chronic pain,

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and psychiatric disorders tend to co-occur, and the presence of more than one psychiatric disorder is significantly associated with increased pain-related disability (APA, 2020; McWilliams et al., 2003). The treatment of pain is complex given the heterogeneity of individuals experiencing pain, the need for multimodal approaches to therapy, a lack of understanding of why individuals transition from acute to chronic pain,[1] and the overlapping effects of pain with depression, anxiety, and other psychosocial conditions (IPRCC, 2016; IOM, 2011). The effective treatment of chronic pain almost always requires multidisciplinary and multimodal approaches.

Opioid Pharmacotherapy Helps Manage Pain but Can Contribute to Adverse Outcomes, Including Mortality

In the mid-1990s, professional societies, patients, and patient advocacy groups argued that there was an epidemic of untreated pain, and wider use of opioid pharmacotherapy was encouraged (Evans et al., 2019; NASEM, 2019). In 1995, the Food and Drug Administration (FDA) approved the controlled-release formulation of OxyContin™ (FDA, 2024), an extended-release semisynthetic opioid produced by Purdue Pharmaceuticals (DEA, 2023; Tompkins et al., 2017; Van Zee, 2009). For a variety of reasons described elsewhere, a marked increase in prescribing of opioid pharmacotherapy occurred in the United States from the mid-1990s to around 2012 (NASEM, 2019; Guy et al., 2017). The populations impacted by changes in access to opioids were not affected equally, with varying outcomes between racial and ethnic groups as well as across different geographic locations (Hirani et al., 2024; NIDA, 2024a; Wilkes et al., 2021; Schieber et al., 2019).

Although opioid pharmacotherapies are prescribed to control pain, they are known to produce feelings of euphoria and sedation, which may contribute to opioid misuse and increased risk of overdose and other drug-related problems (Schuckit, 2016). However, rapid increases in opioid medication dosage can inhibit respiration and even lead to death (Schuckit, 2016). Receiving higher amounts of morphine milligram equivalents is associated with increased risk of tolerance, dependence, OUD,[2] overdose, mortality, and suicide.

Increases in opioid medication prescribing coincided with rising mortality from OUD. Between 2001 and 2016, U.S. opioid-related mortality increased by 345 percent, from 9,489 to 42,245 deaths (NIDA, 2024b; Gomes et al., 2018; Bohnert et al., 2011). In 1999, the number of deaths due to opioid overdose (excluding non-methadone synthetics) was 3,300 (1.2 per 100,000 population), increasing to 12,195 (4.0 per 100,000) by 2007, reaching its peak in 2011 at 14,251 (4.6 per 100,000) and then decreasing to 8,263 (2.4 per 100,000) in 2019 (NIDA, 2024b). Studies also document an increasing risk of suicide (fatal or attempted) during this same period (Fenton et al., 2022; Oliva et al., 2020; Ashrafioun et al., 2019; Gordon and Volkow, 2019). These trends are compounded by the increased use of illicit synthetic opioids, which are now the main drivers of drug overdose deaths (CDC, 2023).

The Co-Occurrence of Opioids and Benzodiazepines in Overdose Death Raised Concerns About Co-Prescribing

Whereas opioid pharmacotherapy is primarily prescribed for pain, benzodiazepine pharmacotherapy is typically prescribed for anxiety, panic disorders, insomnia, and to reduce seizures (Edinoff et al., 2021; FDA, 2020; Lembke et al., 2018; Olfson et al., 2015). Between 2002 and 2014, the percentage of outpatient individuals nationally prescribed both opioid and benzodiazepine pharmacotherapies increased from 6.8 to 9.6 percent, with more than half of individuals receiving both prescriptions from the same prescribers (NASEM, 2019; Hwang et al., 2016). Since 2016, the percentage of patients co-prescribed these pharmacotherapies has decreased (IQVIA Institute, 2020). In the United States, the percent of individuals with a concomitant prescription continued its decline, from 10.5 percent in 2017 to 8.3 in 2019.[3]

[1] Acute pain defined as pain, usually resulting from injury, surgery, or trauma, that lasts for less than 3 months, disappearing when the underlying cause is treated (IASP, 2021). Chronic pain is defined as pain persisting longer than the expected, such as at least 3 months, for healing or pain (IASP, 2021; NASEM, 2019; Treede et al., 2019; Rosenblum et al., 2008; Ashburn and Staats, 1999).

[2] The *Diagnostic and Statistical Manual of Mental Disorders* defined OUD as "a problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the [11 diagnostic criteria], occurring within a 12-month period" (APA, 2013).

[3] Dr. Christopher Jones. Presentation to the committee on March 9, 2023. Trends in Opioid and Benzodiazepine Use, Misuse, and Overdose.

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BOX 1-1
Physiology of Respiratory Depression

Our understanding of the control mechanisms for respiration and what can lead to respiratory depression has progressed substantially in the last 30 years. The control of respiration is a critical component of maintaining the homeostatic conditions necessary for life. The primary sites of respiratory control are the brain stem and peripheral sensors, specifically the carotid body. The three primary blood-level drivers of breathing are hypercapnia (increasing amounts of carbon dioxide), lower Ph (increased amount of acidity), and hypoxia (lack of sufficient oxygen). A number of drugs affect one or more of these components, and combined effects can lead to greater suppression that potentially leads to respiratory arrest and death.

Opioids have been shown to directly suppress the sensitivity of central chemoreceptors to CO_2 in the medulla, resulting in suppression of the respiratory response to blood carbon dioxide levels in a dose-dependent manner in normal individuals (Radke et al., 2014; Cepeda et al., 2001). At higher doses, opioids also lead to central nervous system (CNS) depression that reduces overall brain activity, including the respiratory center's response to hypoxia (lower oxygen levels), which can lead to respiratory arrest and death. Benzodiazepines are not known to have direct effects on the respiratory centers at normal doses in normal individuals (Mak et al., 1993). At higher doses, they do cause dose-dependent CNS depression by reducing overall brain activity, including respiratory centers, which can lead to respiratory depression. The amount of respiratory depression is variable across drugs and individuals, especially with the more rapid-onset intravenous administration of drugs, such as midazolam (Murciano et al., 1993; Forster et al., 1983). These components of respiratory depression are the most apparent when treating people who are drug naïve and need acute therapy, such as perioperatively. Given the substantial variability in patients' responses to opioids and benzodiazepines, careful monitoring of patients in the post-anesthesia care unit is imperative to prevent clinically relevant respiratory depression.

In chronic use, the relationship is more complex, with a demonstration of significant tolerance to opioid respiratory depression (Algera et al., 2021) and reduction in receptor sensitivity in chronic benzodiazepine users (Potokar et al., 1999). While the risk of respiratory depression can be quite different than that seen in acute use (Teichtahl et al., 2005), it remains a potential danger in overdose situations when the doses taken are substantially higher than the patient's usual dose.

The combination of opioid and benzodiazepine pharmacotherapies is known to have potential adverse respiratory effects, as the sedating effects of benzodiazepines can further suppress breathing in individuals experiencing opioid-induced respiratory depression (Box 1-1). Data on causes of death in overdose fatalities collected and published by the National Institute of Drug Abuse indicate that the percent of overdose deaths with concomitant benzodiazepine pharmacotherapy rose dramatically in the initial period of the opioid epidemic from 1999 to 2010, maintaining its peak through 2012, and has been falling slowly since (NIDA, 2023; Guy et al., 2017). However, the level of risk and the relationship of these deaths to the concomitant prescribing of opioid and benzodiazepine pharmacotherapies compared to the use of other pharmacotherapies has never been carefully studied.

Using 2013–2014 Medicare Part D data, Hernandez and colleagues (2018) found that in the first 90 days of concomitant use of opioid and benzodiazepine pharmacotherapies, the risk of opioid-related overdose was five times greater than among those using only opioid pharmacotherapy (NASEM, 2019). Overdose mortality resulting from concomitant benzodiazepine and opioid pharmacotherapies more than doubled from 2007 to 2019, although the percentage of all overdose deaths due to benzodiazepine and opioid pharmacotherapies have increased slightly (10.0 to 11.8 percent). Between 2007 and 2019, the percent of overdose deaths attributable to benzodiazepine and synthetic opioid medications (not methadone) increased (from 1.2 to 7.3 percent) (NIDA, 2023).

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Pain and Opioid Prescribing in the Veteran Population

Studies have demonstrated that a higher percentage of veterans[4] experience pain compared to non-veterans (civilians), which is attributable to the physical demands of military service, including training and combat-related injuries (Reif et al., 2018; Nahin, 2017; Gironda et al., 2006; Clark, 2004). Veterans[5] are also more likely to experience chronic health conditions, psychological distress, and a higher incidence of suicide than non-veterans (Moore et al., 2023; VA, 2018; Nahin, 2017; Kramarow and Pastor, 2012). As a result, veterans are more likely than the general population to need care for chronic pain and other conditions.

About 9 million U.S. veterans receive health care services from the Veterans Health Administration (VHA) each year (VA, 2023). The VHA is the largest integrated U.S. health care network, with over 1,300 health care facilities, including over 170 medical centers and 1,100 outpatient clinics (VA, 2024). Through the VHA's integrated health care system, eligible veterans can receive the full array of health care services, including primary, specialty, and tertiary care. Additional services and care for eligible veterans include home health, long-term care, and coverage for prescriptions and prosthetic devices. The VHA also provides mental health services for post-traumatic stress disorder (PTSD), military sexual trauma, depression, and problems with substance use.

VHA veterans (those who obtain care through the VHA) differ from non-VHA veterans (veterans who obtain health care from non-VHA health care providers). Compared to non-VHA veterans, VHA veterans had a twofold higher prevalence of physical health conditions and mental health disorders[6] (such as PTSD), as well as anxiety and depression, even after adjusting for demographic characteristics (Meffert et al., 2019; Eibner et al., 2015; Kramarow and Pastor, 2012). In addition, a third of VHA veterans reported chronic pain; furthermore, VHA veterans are found to be more likely than non-VHA veterans to have chronic pain (45.2 percent versus 26.8) (Mannes et al., 2022). Among VHA veterans, the rate of OUD was 7 times higher than that of non-VHA veterans (Ahonle et al., 2020).

Similar to national trends, the prevalence of receiving an opioid prescription increased within the VHA[7]—from 18.9 percent of individuals in 2004 with at least one outpatient VHA visit and a history of regular VHA medication to 33.4 percent in 2012 (Mosher et al., 2015). Studies have demonstrated that opioid prescribing slowed in the VHA from 2012 to 2020 (Hadlandsmyth et al., 2018; Gellad et al., 2017) and was reduced overall by 64 percent (VA, 2020).

In considering the co-prescribing of opioid and benzodiazepine pharmacotherapies between 2004–2009, one study found that 27 percent of VHA veterans received both drugs and accounted for nearly half of the opioid-related overdose deaths (Park et al., 2015). Another study compared the risk of adverse outcomes (accidents and injuries, non-fatal overdose events, and death) in VHA veterans who received a long-term opioid prescription only[8] (N = 924,656) to VHA veterans (N = 110,305) concurrently prescribed opioid and benzodiazepine pharmacotherapies. VHA veterans with co-prescriptions had a 35.9 percent higher risk of experiencing an adverse outcome (e.g., opioid-related overdose, self-inflicted injuries, all-cause mortality) compared to long-term opioid prescriptions alone (Gressler et al., 2018).

[4] See also Appendix G for perspectives from the Department of Veterans Affairs PAIN/Opioid CORE Veteran Engagement Panel.

[5] The National Health Interview Study defines veteran status using two questions: "Are you currently in the armed forces?" Individuals responding "yes" are coded as active military. Individuals responding "no" are then asked: "Have you ever served on active duty in the U.S. Armed Forces, Military Reserves, or National Guard?"

[6] Mental health disorders included ICD-9 codes 290–310, 311, and V11 (Eibner et al., 2015).

[7] Opioid prescription based on the receipt of an opioid prescription, using VHA outpatient prescription fill (Mosher et al., 2015).

[8] Individuals receiving long-term opioid prescription were categorized as "chronic" or "high-risk." "Chronic" was defined as receiving a 90-day or greater opioid prescription, with less than a 30-day gap in supply and within a 180-day period. "High-risk" was defined as those with ≥1 substance use disorder diagnosis (excluding tobacco) and/or an average opioid dose of ≥100 morphine milligram equivalent/day (MME/day). Concomitant prescribing was defined as the receipt of both opioid and benzodiazepine prescriptions, with a >7 days of overlap of both prescriptions.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

CONGRESSIONAL MANDATE TO ADDRESS CONCERNS ABOUT PRESCRIBING OPIOIDS AND BENZODIAZEPINES IN THE VETERAN POPULATION

The concerns of the U.S. Congress drew attention to two concurrent public health issues, the high prevalence of pain with evidence of less-than-optimal pain management and high rates of excessive prescription and nonprescription opioid use, misuse, OUD, and their related harms, including overdose and mortality, especially related to veterans. In 2019, through the Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019 (Hannon Act),[9] Congress mandated that the Department of Veterans Affairs (VA) request an ad hoc committee of the National Academies be assembled to "to evaluate the effects of opioids and benzodiazepine on all-cause mortality of veterans, including suicide, regardless of whether information relating to such deaths has been reported by the Centers for Disease Control and Prevention." The Hannon Act requested "a revised study design to fulfill the goals of the 2019 study design of the National Academies." The protocols conducted for this report reflect the study designs presented in the congressionally mandated 2019 National Academies report[10] *An Approach to Evaluate the Effects of Concomitant Prescribing Opioids on Veteran Deaths and Suicides*.

The 2019 National Academies report outlined the target trial emulation (TTE) framework in its proposed study designs to emulate, using observational data, randomized controlled trials (RCTs). RCTs represent the gold standard for identifying reliable causal effects of an intervention, such as medication effects on important outcomes. Given the exposure (opioid and benzodiazepine pharmacotherapies) and outcomes of interest (all-cause mortality and suicide mortality), RCTs have ethical and feasibility barriers in responding to the statement of task. The 2019 National Academies report proposed two study designs ("opioid treatment initiation" and "opioid tapering") to address the effect of prescribed opioid pharmacotherapy on all-cause mortality and suicide mortality. In the report, the committee outlined specific study components to consider: eligibility criteria, treatment strategies, treatment assignment, start and end of follow-up, outcomes, causal contrasts, and statistical approach.

STATEMENT OF TASK

In response to the congressional mandate, the National Academies convened a 13-member committee with expertise in pain, mental health, neurology, addiction, epidemiology, pharmacoepidemiology, statistics, VHA health data systems, and VHA and non-VHA care of mental health and pain in veterans. The committee held 11 meetings over 18 months. In addition, the committee engaged with the Veteran Engagement Panel of the VA's Health Systems Research Pain/Opioid Consortium on Research and appreciates the veterans who shared their lived experiences of managing pain (more details in Appendix G).

This committee leveraged and refined the 2019 National Academies report's proposed TTE protocols to respond to the statement of task. The committee developed causal research questions to align with the statement of task and refined the TTE protocols to make use of available observational electronic health record (EHR) data, data from VHA administrative and clinical databases, and mortality data from the National Death Index. For the complete statement of task, see Box 1-2.

APPROACH TO THE TASK AND ORGANIZATION OF THE REPORT

Committee Interpretation of Statement of Task (Causality Questions)

To better understand the task and sponsor expectations, the committee sought clarifications from the VA and Congress before initiating modifications to the study designs. Additionally, the committee sought clarifications from the VA regarding the quality and comprehensiveness of available data to select the best primary outcome for the studies and assess the availability of data necessary to study the effects of tapering on all-cause mortality and suicide mortality using the protocol outlined by the 2019 committee as the starting point. After these clarifications, the committee interpreted the congressional mandate as a desire to refine and implement the 2019 protocol

[9] Public Law 116-171, 116th Congress, October 17, 2020.

[10] Mandated by the Consolidated Appropriations Act, 2018, Number 115-141, Session: 115th Congress (Second Session).

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BOX 1-2
Statement of Task

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will evaluate the effects of opioid and benzodiazepine use on all-cause mortality of U.S. veterans, including suicide, regardless of whether information relating to such deaths has been reported to the U.S. Centers for Disease Control and Prevention. Specifically, the committee will quantify the effects of opioid and benzodiazepine prescribing on the risk of death among veterans who received care from the Department of Veterans Affairs (VA) between 2007 and 2019. In their analysis, the committee will focus on:

(a) the effect of opioid prescribing for pain, relative to alternative non-opioid pain treatments,

(b) the effects of higher doses relative to lower doses of opioids,

(c) the effect of co-prescribing a benzodiazepine among patients already receiving opioids, relative to alternative treatments for anxiety and other indications for benzodiazepines, and

(d) the effect of initiating opioids among patients already taking benzodiazepines.

to additionally assess the impact of concomitant prescribing of opioid and benzodiazepine pharmacotherapies on all-cause mortality and suicide mortality in veterans.

To address the research questions, the current committee chose to propose TTE protocols and corresponding observational studies. The committee agrees with the 2019 committee that while one or more RCTs could be conducted to answer questions about the comparative effectiveness or safety of opioid and benzodiazepine pharmacotherapies, RCTs are impractical for studies, particularly those posing ethical dilemmas (e.g., administering opioids) (NASEM, 2019; Armstrong, 2012). The committee also agreed that observational data could be analyzed to approximate an RCT when conducting an RCT was not possible or practical. The 2019 committee proposed applying the TTE framework, an approach that leverages observational data to emulate an RCT, to examine the effect of prescribed opioid and benzodiazepine pharmacotherapies on mortality. The 2019 report laid out proposed trial protocols, which have been leveraged for the studies conducted in the current report. The present committee refined the causal research questions that align with the VA statement of task and refined the TTE protocols (e.g., eligibility criteria, treatment strategies, outcomes, analysis plan), using available observational EHR data from the VA administrative and clinical databases and mortality data from the National Death Index. Causal inference from large observational databases can be viewed as an attempt to emulate an RCT to answer the researchers' question of interest (NASEM, 2019; Hernán and Robins, 2016).

Considering the available data, the committee operationalized the statement of task into the following causal questions, which are addressed in three distinct studies:

- Among veterans receiving care in the VHA who were not consistently[11] dispensed[12] pain pharmacotherapy between 2007 and 2019, what is the effect of newly dispensed[13] opioid versus non-opioid pain pharmacotherapy on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) among those without and with current use of benzodiazepine pharmacotherapy within a 12-month follow-up period? (Study 1)

[11] Not dispensed any qualifying opioid or non-opioid pain pharmacotherapy in the 90-day pre-index period.

[12] The committee notes differences in types of pharmacy data measures. Pharmacy data can be categorized into three measures: *prescribed* (prescriber submits a prescription to a pharmacy), *filled* (pharmacy completes the requested prescription), and *dispensed* (individual picks up/is mailed the prescription from the pharmacy). The committee used dispensed pharmacy data in its analyses.

[13] The committee operationalized the term "initiation" in the statement of task as "newly dispensed" pharmacotherapy in analyses. In the committee's studies, "newly dispensed" was defined as pharmacotherapy of interest not dispensed (or initiation of pharmacotherapy) to the individual in the 90 days before the start date.

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- Among veterans receiving care in the VHA newly dispensed full agonist[14] opioid pharmacotherapy between 2007 and 2019, what is the effect of different initial opioid dosage and escalation strategies on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) within a 12-month follow-up period? (Study 2)
- Among veterans receiving care in the VHA who were consistently dispensed opioid pharmacotherapy between 2007 and 2019, what is effect of newly dispensed benzodiazepine versus alternative non-benzodiazepine pharmacotherapy for anxiety and other common indications for benzodiazepines on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) within a 3-month follow-up period? (Study 3)

Topics Not Included in the Statement of Task

For all studies, the committee did not include "chronic pain" in the causal question or as a covariate for several reasons. There are multiple factors that limit the reliability of pain-relevant diagnosis codes and their utility in observational research. First and foremost, there are challenges in its measurement and capture, such as potential underreporting of the large variety of diagnoses associated with chronic pain diagnoses and the underlying painful conditions. Preliminary analysis indicated that 37.7 percent of eligible participants who were dispensed an opioid pharmacotherapy did not have a diagnosis code related to chronic pain as defined in Mayhew et al., 2019. Accurate diagnosis can be complicated and emerge over time as a comprehensive assessment proceeds (e.g., diagnosis of low back pain). Further, providers may vary in the reporting of pain-relevant diagnostic codes, which may further contribute to unreliability. Additionally, individuals with chronic pain report multiple sites of pain and multiple pain conditions, further complicating the use of diagnosis codes to characterize the pain experience and to reliably associate diagnosis with treatment decisions (Edwards et al., 2016). Yet, opioid pharmacotherapy is used for a wide variety of pain conditions (Pasricha et al., 2018). Given the challenges in capturing pain and chronic pain, the committee assumed that most individuals who were dispensed an opioid prescription received it to manage pain (via opioids' known analgesic effects). The indication of pain was used to choose the non-opioid pharmacotherapies included in study 1, to control for confounding by indication. Finally, the term is not reflected in the statement of task.

The committee noted that there are several aspects of opioid prescribing that were not stated in the statement of task and not reflected in the committee's analyses. The committee did not implement the opioid tapering trial protocol suggested in the 2019 report, considering the following factors in its decision. First, the current statement of task did not direct the committee to examine the effect of opioid tapering on mortality. Second, the committee was aware of studies based on the 2019 report protocol that had been or were being completed and commissioned a review of these and other relevant studies conducted since the 2019 report (see Appendix E). Based on the review, the committee determined that the risk of immortal time and selection biases is high and substantially limits the extent to which retrospective observational studies can infer causality between opioid tapering and mortality. Of note, Dr. Erin Krebs and her colleagues applied the 2019 protocol in an unpublished study (see Appendix F) included in the review. It was noted that the study's findings and conclusions were highly sensitive to different study design, statistical modeling, and measurement strategies. In addition, the treatment assignment was based on pharmacy records and as such may not accurately reflect whether a tapering was intended or actually took place. Based on these observations, not available at the time of the 2019 report, the committee concludes that additional efforts to implement such a study is unlikely to yield more definitive results and, for these reasons, the committee chose not to implement the tapering trial suggested in the 2019 report. The committee focused the main report to reflect findings from the analyses addressing the statement of task.

The statement of task also did not direct the committee to compare mortality of veterans prescribed opioids and benzodiazepines in the VHA to veterans prescribed opioids and benzodiazepines in other health care systems.

[14] There are two types of opioids: full agonist and partial opioid agonist. Full opioid agonists fully activate the mu brain receptors, enabling the opioid to have "full" effect, such as morphine, codeine, oxycodone, and fentanyl. Partial opioid agonists also activate mu receptors in the brain but to a lesser degree, such as butorphanol or tapentadol.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Thus, comparing VHA and non-VHA providers was not part of the committee's work. In addition, the committee notes that the focus of the statement of task is to examine the risk, not the benefits, of opioid and benzodiazepine prescribing. The committee did not investigate the impact of non-pharmacological approaches to pain treatment on all-mortality, including suicide mortality, as this was outside the scope of the statement of task.

Furthermore, the committee notes that the statement of task specifically mandated the study period (2007–2019) to understand the implications of opioid treatment on mortality in veterans. Therefore, the findings of this report are not intended to be applicable to current practices or behaviors, including those of the VHA. In addition, these retrospective studies are inherently forensic, reflecting the effect of care that occurred in the past rather than being indicative of the mortality risks of current practices, particularly given the ongoing changes in opioid prescribing practices, the policy landscape, mental health care, and the nature of the opioid overdose epidemic in the intervening years.

The report is laid out the following way. Chapter 2 provides a detailed overview of the policies, regulations, and clinical practice guidelines regarding prescribing opioids and benzodiazepines released during, and around, the study period (2007–2019).

Chapter 3 sets the stage of the methodological approach taken to address the statement of task, especially the application of the TTE framework. The chapter describes the data sources used, medications selected, and inclusion rationale for the studies. In addition, the committee's specifications for the target trial components (e.g., eligibility criteria, treatment strategies and assignments, statistical analyses) are outlined. Specific and detailed information on each of the target trial specifications is found in Chapters 4, 5, and 6.

Chapters 4, 5, and 6 outline the details of each TTE to address the statement of task. All studies examine two outcomes: all-cause mortality (primary outcome) and suicide mortality (secondary outcome). Study 1 examines the effect of the initiation of opioid versus non-opioid pain pharmacotherapy[15] (e.g., non-steroidal anti-inflammatory drugs) among those without (study 1a) and with (study 1b) current benzodiazepine pharmacotherapy. Study 2 employs two target trials: study 2a assesses the effect initial opioid dosage at baseline, and study 2b assesses the effect of escalating dosage strategies. Study 3 examines the effect of newly dispensed benzodiazepine pharmacotherapy versus alternative non-benzodiazepine pharmacotherapy among veterans consistently dispensed opioid pharmacotherapy.

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[15] The committee used the term "pharmacotherapy" throughout the report instead of "medications," "prescriptions," or "treatment," especially when referencing the committee's analyses and results.

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2

A History of the Policy Landscape

STRATEGIES IMPLEMENTED TO COMBAT THE OPIOID EPIDEMIC

This chapter provides a comprehensive, though not exhaustive, overview of the changing landscape around clinical guidelines and policies related to opioid prescribing since the mid-1990s. In addition to national efforts, this overview demonstrates early guidelines set forth by the Veterans Health Administration (VHA) in 2003 to support clinical decision making around pain management and opioid treatment. VHA clinical guidelines continued to evolve and were subsequently updated (2010, 2017, 2022) along with the agency-wide Department of Veterans Affairs (VA) Opioid Safety Initiative initiated in 2013, which, among many efforts, increased education and monitoring and promoted safe and effective prescribing. These efforts were complemented by other federal agency and state efforts, such as additional clinical guidelines from the Centers for Disease Control and Prevention (CDC) in 2016 and 2022 and the Department of Health and Human Services (HHS) in 2019. In addition, federal legislation was enacted during this time frame, such as the Veterans Access, Choice, and Accountability Act (2014), the Comprehensive Addiction and Recovery Act (2016), and the VA Mission Act (2018), to help support veterans and/or fight the opioid epidemic. The committee recognizes that understanding the policy landscape and how the implementation of new policies changed practices over time is crucial. This chapter describes the context for what individuals faced seeking relief from pain and support from providers and the health care system. Additional policy details are in Appendix D.

Early Attitudes Toward Prescribing Opioids and Pain Management

Attitudes toward managing pain in the mid-1990s and 2000s helped contribute to increased trends in opioid prescription. In 1995, the American Pain Society coined the phrase "pain as the fifth vital sign" (Campbell, 1995). Furthermore, in 1999, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO)[1] approved standardized pain assessment and management of all patients, which was required to be incorporated into policies of health care organizations and providers to obtain JCAHO-accreditation (Baker, 2017; Ahmedani et al., 2014).

[1] A U.S, based nonprofit organization that accredits more than 22,000 health care organizations and programs in the country. (https://www.jointcommission.org/).

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

These new standards[2] went into effect in 2012. In 1999, the VHA followed the American Pain Society recommendations, integrating the Pain as the 5th Vital Sign Initiative into the VHA National Pain Management Strategy, whereby routine screening, a published comprehensive pain assessment and management toolkit, and educational campaigns were launched (VA, 2000, 2018b; Mularski et al., 2006; Cleeland et al., 2003; Kerns et al., 2000). In addition, given efforts to improve pain management in patients and the pharmaceutical industry's push of the use of opioid pharmacotherapy, several organizations, such as the Federation of State Medical Boards and Drug Enforcement Administration, reduced oversight and scrutiny to encourage providers to prescribe opioids to address the unmet needs of chronic pain patients (Tompkins et al., 2017; Van Zee, 2009).

Relevant Clinical Guidelines, Policies, Legislation

Guidelines, policies, and legislation have affected opioid prescribing practices within the context of changing attitudes toward pain management. To provide context, the committee reviewed several VA policies, VA clinical guidelines, and federal legislation that had an impact on opioid prescribing, including by VHA providers, and support for veterans during the study period (2007–2019). In addition, guidelines from other agencies, such as CDC and HHS, were also reviewed (Dowell et al., 2016, 2022; HHS, 2019). Table 2-1 outlines these efforts and includes a summary of VA clinical practice guidelines (CPGs) (inform clinical decision making within the VHA), VHA directives (outline mandatory department policies), federal legislation, and other relevant guidelines or efforts within the VA or of other agencies. Figure 2-1 depicts a timeline of key policies implemented by the VA, various federal agencies, and the federal government between 2001 and 2024.

This chapter is a brief summary of dynamic changes in the attitudes, policies, and CPGs that occurred during the study period of interest. Appendix D provides further detail of the policies and legislation outlined in Table 2-1 as well as other efforts, such as FDA's Opioids Analgesic Risk Evaluation and Mitigation Strategies and state Prescription Drug Monitoring Programs. Given the dynamic aspects of opioid and benzodiazepine prescribing during the study period, the committee adjusted for these factors in the analytic models (see chapter 3 for more details, section on *Accounting for Secular Trends and Variation by Facility*).

[2] In 2009, assessment of pain in all patients, except for those receiving behavioral health care, was eliminated as a standard, given concerns that the standards encouraged opioid use (Baker, 2017).

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 2-1 Opioid Policy Landscape

Opioid-Related Policy and Programs	Year Established	Summary	Source
Prescription Drug Monitoring Program (PDMP)	1939–[1]	Controlled substance monitoring database.	State
VHA National Pain Management Strategy	1998	Established pain management as a national priority. Aims to provide a systemwide standard of care for preventable pain. Includes the Pain as the 5th Vital Sign Initiative.	VHA
Department of Veterans Affairs (VA)/Department of Defense (DoD) Clinical Practice Guidelines (CPGs) for the Use of Opioids in the Management of Chronic Pain	2003	VA clinician guidelines for opioid initiation, dose, tapering, and assessment and risk management.	VA
Veterans Health Administration (VHA) Directive 2009-053: Pain Management	2009	Outlined essential components of high-quality pain care: (1) timely and appropriate pain assessment, (2) development and enactment of a pain treatment plan, and (3) subsequent reassessment of the effectiveness of the plan. Led to the VHA's Stepped Care Model for Pain Management (SCM-PM).	VA
VA/DoD Clinical Practice Guideline-Management of Opioid Therapy for Chronic Pain	2010	Updated VA clinician guidelines for opioid initiation, dose, tapering, and assessment of use and risk management.	VA
VA Opioid Safety Initiative (OSI)	2013	VA systemwide initiative (strategies include education, pain management, risk mitigation, addiction treatment) to address the opioid crisis.	VA
Veterans Access, Choice, and Accountability Act[2]	2014	Federal legislation to expand options for veterans to receive care from non-VA providers, also known as the "Veterans Choice Program (VCP)."	Legislation
VHA Directive 1005: Informed Consent for Long-Term Opioid Therapy for Pain	2014	VA directive requiring education for patients and informed consent is required for long-term opioid therapy for pain.	VA
Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain—United States	2016	CDC clinical guidelines for prescribing opioid pharmacotherapy in primary care patients. Advises against opioid and benzodiazepine co-prescribing.	CDC
U.S. Food and Drug Administration (FDA) Box Warning	2016	FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepine; requires its strongest warning.	FDA
VHA Directive 1306: Querying State Prescription Drug Monitoring Programs	2016	VA directive that requires providers to query the PDMP for patients receiving a controlled substance prescription.	VA

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 2-1 Continued

Opioid-Related Policy and Programs	Year Established	Summary	Source
Comprehensive Addiction and Recovery Act[3]	2016	Federal legislation requiring VA to • Submit patient data to state PDMPs, • Ensure VA prescribers have access to their own state's PDMP, • Expand OSI to non-VA facilities caring for veterans, • Address veteran pain management.	Legislation
VA/DoD Clinical Practice Guidelines for the Use of Opioids in the Management of Chronic Pain	2017	Updated VA clinician guidelines for opioid initiation, dose, tapering, and assessment and risk management. Incorporates advice recommending against the co-prescribing of opioids and benzodiazepines.	VA
VA/DoD Practice Guideline for the Management of Posttraumatic Stress Disorder (PTSD)	2017	VA clinician guidelines and recommendations for veterans with acute stress reaction/disorder, the assessment and diagnosis of PTSD, and the management of PTSD. Recommends against the routine use of benzodiazepines in veterans with PTSD.	VA
VA Mission Act [4]	2018	Enhanced ability for eligible veterans to access health care from non-VHA providers.	Legislation
Substance Use Disorder Prevention That Promotes Opioid Recovery and Treatment for Patients and Communities Act[5]	2018	In Section 399O(a)(1)(ii)(II(c)), enhances state PDMP by linking to other state providers' prescribing data, such as VHA facilities.	Legislation
U.S. Department of Health and Human Services (HHS) Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics	2019	HHS clinical guidelines in reducing opioid dosage or discontinuing LTOT for chronic pain.	HHS
Veterans Community Care Program	2019	Per Mission Act, VA program to further enhance veterans' access to non-VA health care providers, replacing the VCP.	VA
VA/DoD Clinical Practice Guidelines for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea (OSA)	2019	Provides a general guide to best practices in the assessment, diagnosis, treatment and management for service members or veterans with chronic insomnia disorder and/or OSA.	VA/DoD
VA Consensus Paper: Alternatives to Opioids for Acute Pain Management After Dental Procedures	2021	VA consensus paper that reviews the evidence and recommends non-opioid pain pharmacotherapy to manage pain after dental procedures.	Wehler et al., 2021
VA/DoD Clinical Practice Guidelines for the Use of Opioids in the Management of Chronic Pain	2022	Updated VA clinician guidelines for opioid initiation, dose, tapering, and assessment and risk management.	VA/DoD

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 2-1 Continued

Opioid-Related Policy and Programs	Year Established	Summary	Source
CDC Guideline for Prescribing Opioids for Chronic Pain—United States	2022	Updated CDC clinical guidelines for prescribing opioid pain medication in primary care patients; incorporates HHS clinical opioid tapering guidelines (2019).	CDC

[1] California became the first state to implement a PDMP program in 1939.
[2] Public Law 113-146, Veterans Access, Choice and Accountability Act of 2014, 113th Congress, August 7, 2014.
[3] Public Law 114-198, Comprehensive Addiction and Recovery Act of 2016. 114th Congress, July 22, 2016.
[4] Public Law 115-182, VA Mission Act of 2018, 115th Congress, June 6, 2018.
[5] Public Law 115-271, Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT), 115th Congress, October 24, 2018.

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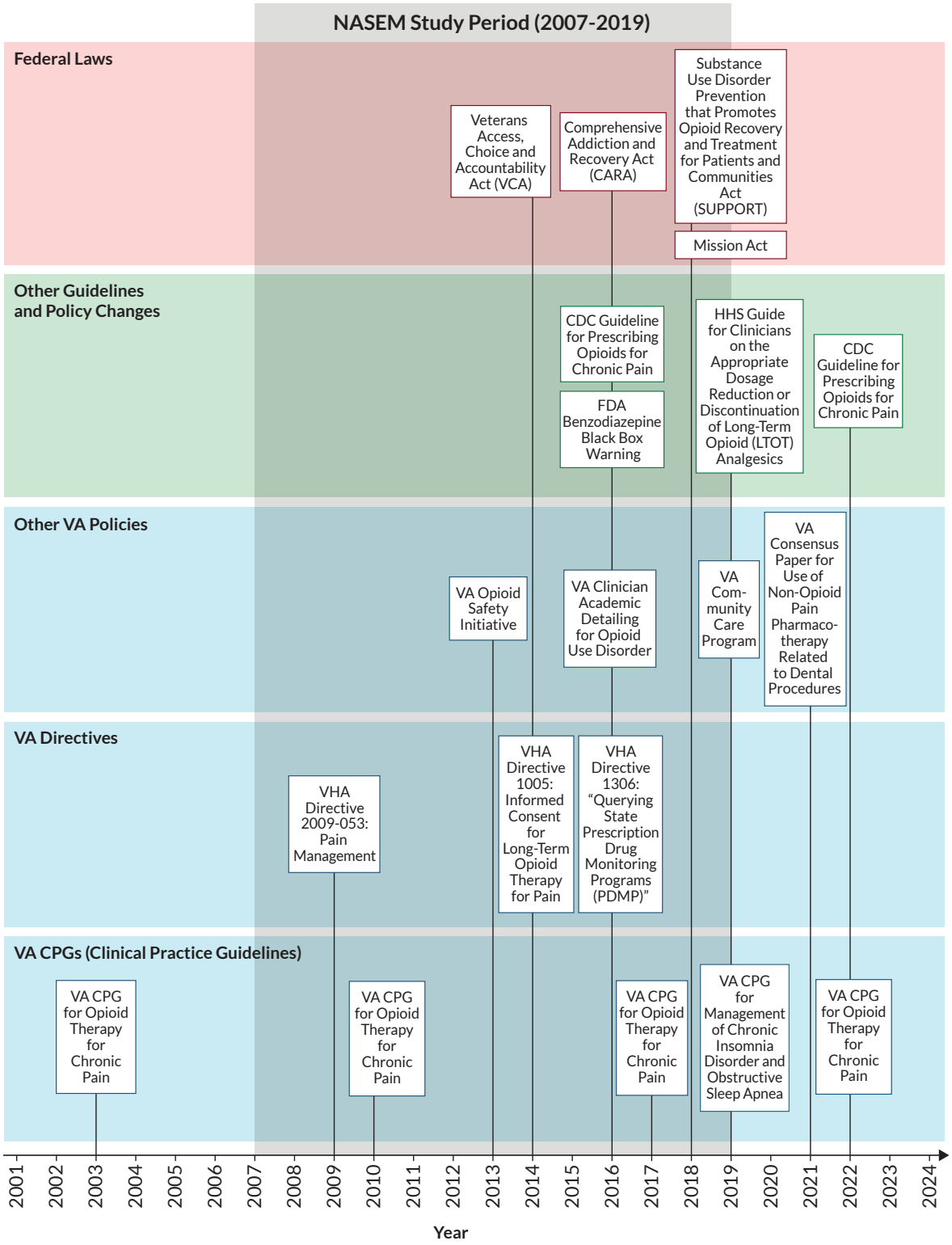

FIGURE 2-1 Timeline of relevant federal laws, clinical guidelines, and policies related to opioid prescribing in the United States (2001–2024).
NOTES: FDA = Food and Drug Administration; HHS = Department of Health and Human Services; NASEM = National Academies of Sciences, Engineering, and Medicine; VA = Department of Veterans Affairs; VHA = Veterans Health Administration.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

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3

Setting the Stage

INTRODUCTION

This chapter provides background for a broad audience and lays out the committee's approach and rationale for using the target trial emulation (TTE) framework to address the effect of prescribed opioid pharmacotherapy[1] on all-cause mortality and suicide mortality. In addition, it presents the common aspects of the study design applied across each of the emulated target trials[2] in the report.

TARGET TRIAL EMULATION FRAMEWORK

In line with the 2019 National Academies report, the current committee employed a TTE framework. A TTE framework is applied in the observational studies to mirror a randomized trial. Randomized controlled trials (RCTs) are experimental studies in which participants are randomly assigned, or randomized, to treatment strategies (Mansournia et al., 2017a). Randomization of a treatment minimizes confounding and assures balance across treatment groups (NASEM, 2019). While RCTs[3] are the gold standard for assessing the causal effects of medical treatments, they often face practical, ethical, cost, and feasibility barriers to implementation. These include prohibitively high costs and time demands, ethical dilemmas around the random allocation to medications with potentially negative side effects, potential for mistreatment of historically vulnerable populations, and potentially small sample sizes in the case of rare medical disorders (Goldstein et al., 2018). At the same time, clinicians and policy makers also need to decide about medical treatments that are not amenable to study in RCTs and must utilize the best available evidence.

In the last three decades, notable progress has been made in estimating the causal effects of medical treatment beyond the confines of RCTs. Approaches that leverage observational data, or data from non-experimental studies (non-RCTs), to analyze the effects of these treatments in the most rigorous way possible are critical. One advance in the modern causal inference literature is the approach of designing an observational study to mimic a

[1] The committee uses the term "pharmacotherapy" throughout the report instead of "medications," "prescriptions," or treatment, especially when referencing the committee's analyses and results.

[2] The committee uses the terms "emulated target trial" and "study" synonymously when referring to the committee's studies and corresponding analyses.

[3] A key advantage of RCTs is protocol-based outcomes ascertainment, which is a limitation with observational studies. This ascertainment can help reduce bias due to misclassification of outcomes, exposure, and confounders.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

hypothetical randomized experiment, or target trial. TTE is an approach that helps ensure the observational study compares realistic clinical treatment strategies, avoids biases related to mishandling time zero, and improves upon conventional methods to address baseline and time-varying confounding (Hernán et al., 2022; Hernán and Robins, 2016). TTE has played a role in rectifying historical discrepancies between observational and randomized results, as seen in instances such as estrogen replacement therapy and risk of cardiovascular disease (Hernán et al., 2008).

With the increasing availability of administrative and clinical health data, such as electronic health records (EHRs) and health insurance claims, there are growing interests in leveraging these observational data to conduct analyses to estimate causal effects. These are most useful in addressing critical medical and public health questions where RCT evidence is not feasible or available. These datasets can have the advantage of being readily available and have large sample sizes to study heterogeneity of effects (Hubbard et al., 2024). Although applying modern causal inference methods using EHR or administrative data may still result in biases due to the lack of randomization, evidence suggests that rigorously designed and conducted emulated trials can yield valid and actionable evidence when RCTs are unavailable (Wang et al., 2023). In a 2023 study by Wang and colleagues, 32 target trials, using observational data, emulated the design of 32 corresponding, high-quality RCTs. The effect estimates were similar between the two approaches, especially when the target trial design elements were closely matched with those in the RCTs (Wang et al., 2023). Thus, both RCTs and observational studies can facilitate causal inferences.

APPLICATION OF TARGET TRIAL EMULATION FRAMEWORK TO ADDRESS THE STATEMENT OF TASK

Recent literature has helped to establish how causal inference can inform clinical practice. In 2024, *JAMA* published a report outlining an approach to lay out when inferring causality using observational data (Dahabreh and Bibbins-Domingo, 2024). The use of causal language when describing these studies is crucial for effective communication in medical journals. The six core questions are the following:

- What is the causal question?
- What quantity would, if known (causal estimand or causal effect of interest), answer the causal question?
- What is the study design?
- What causal assumptions are being made?
- How can the observed data be used to answer the causal question in principle and in practice?
- Is a causal interpretation of the analyses tenable?

The authors state that adhering to this guidance can facilitate better communication between authors, reviewers, editors, and readers (Dahabreh and Bibbins-Domingo, 2024).

The committee applied the TTE framework, reflecting current best practices in the causal inference methodology field, and addressed the six questions. The approach included precise definitions of the causal objectives and effects, comparing clinically realistic treatment strategies, valid assignment of time zero, and thorough adjustment for baseline and time-varying confounding variables. By using the TTE framework, the committee intended to eliminate common structural biases common in observational studies, such as immortal time bias—which stems from utilizing post-baseline treatment information for treatment assignment—and selection bias, from analyzing prevalent users.

DEVELOPING THE CAUSAL RESEARCH QUESTIONS FROM THE STATEMENT OF TASK

The committee developed causal research questions to align with the four items in the statement of task:

(a) the effect of opioid prescribing for pain, relative to alternative non-opioid pain treatments (study 1),
(b) the effects of higher dosages relative to lower dosages of opioids (study 2),

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

(c) the effect of co-prescribing a benzodiazepine among individuals already receiving opioids, relative to alternative treatments for anxiety and other indications for benzodiazepines (study 3), and
(d) the effect of initiating opioids among individuals already taking benzodiazepines (study 1).

The committee combined tasks (a) and (d) and developed one causal research question (study 1). The committee interpreted both (a) and (d) as examining the effect of initiating opioids on mortality compared to those not initiating non-opioid pain pharmacotherapy. The committee interpreted task (d) as a subset of task (a) in that it further examined the effect of initiating opioids on mortality in those without and with a current benzodiazepine prescription. For task (b), the committee interpreted it as examining the effect of escalation dosage strategies on mortality (study 2). The committee considered two aspects of escalation: the starting, or initial, baseline dosage, and the trajectory, or speed at which dosage can increase over time. The committee interpreted task (c) (study 3) as examining the impact of initiating benzodiazepine pharmacotherapy co-prescribing versus alternative non-benzodiazepine pharmacotherapy on mortality among individuals already receiving long-term opioid pharmacotherapy. The benzodiazepine comparator group are those individuals with conditions, specifically anxiety and insomnia, that can also be treated with benzodiazepine pharmacotherapy.

For all studies, the committee did not include "chronic pain" in the causal question given challenges in its measurement and capture (potential underreporting of both pain and chronic pain diagnoses. Preliminary analysis indicated that 37.7 percent of eligible participants who were dispensed an opioid pharmacotherapy did not have a diagnosis code related to chronic pain as defined in Mayhew et al., 2019, and the term is not reflected in the statement of task. In the causal questions, the term "pain" is only used to specify the non-opioid pharmacotherapies included in study 1. Given the challenges in capturing pain and chronic pain, the committee assumed that most individuals who were dispensed an opioid prescription received it to manage pain. See also Chapter 1 for more details on committee's rationale.

Causal Research Questions

The committee developed three causal research questions to reflect the statement of task:

Study 1: The Effect of Opioid Prescription on All-Cause Mortality, Including Suicide

Among veterans receiving care in the Veterans Health Administration (VHA) who were not consistently dispensed[4] pain pharmacotherapy between 2007 and 2019, what is the effect of newly dispensed opioid versus non-opioid pain pharmacotherapy on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) among those without and with current use of benzodiazepine pharmacotherapy within a 12-month follow-up period?

Study 2: The Effect of Prescribed Opioid Escalation on All-Cause Mortality, Including Suicide

Among veterans receiving care in the VHA newly dispensed full agonist[5] opioid pharmacotherapy between 2007 and 2019, what is the effect of different initial opioid dosage and escalation strategies on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) within a 12-month follow-up period?

[4] The committee notes differences in types of pharmacy data measures. Pharmacy data can be categorized into three measures: prescribed (prescriber submits a prescription to a pharmacy), filled (pharmacy completes the requested prescription), and dispensed (individual picks up/is mailed the prescription from the pharmacy). The committee used dispensed pharmacy data in its analyses.

[5] There are two types of opioids: full and partial opioid agonists. Full agonists fully activate the mu receptors in the brain, enabling the opioid to have "full" effect, such as morphine, codeine, oxycodone, and fentanyl. Partial agonists also activate mu receptors in the brain but to a lesser degree, such as butorphanol or tapentadol.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Study 3: The Effect of Co-Prescribed Opioids and Benzodiazepines on All-Cause Mortality, Including Suicide

Among veterans receiving care in the VHA who were consistently dispensed opioid pharmacotherapy between 2007 and 2019, what is the effect of newly dispensed benzodiazepine versus alternative non-benzodiazepine pharmacotherapy for anxiety and other common indications for benzodiazepines on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) within a 3-month follow-up period?

Causal Effect of Interest

The causal effects of interest are the per protocol effect and the intent-to-treat (ITT) effect. The per protocol effect corresponds to the effect of consistently following the assigned treatment strategy during follow-up. Modern causal inference methods enable estimation of per protocol effect without potential selection bias by conditioning the analysis on those who adhere fully to the treatment regimen during follow-up. The ITT effect, on the other hand, characterizes the effect of initiating the treatment strategy at baseline, irrespective of either cross-over to another exposure group or treatment discontinuation during follow-up. Valid estimation of both ITT effect and per protocol effect require adjustment for preinitiation variables to adjust for confounding related to initial treatment selection. The per protocol effect is as important as the ITT effect; otherwise, treatment strategies with substantial inconsistent use can misleadingly suggest that harmful medications are safe or effective interventions are ineffective.

Estimating the Causal Effects in Each of the Studies

In study 1, the committee conducted both per protocol effect (main) and ITT effect (secondary) analyses to provide a range of estimates capturing the effect of opioid pharmacotherapy—from initiation, without requiring continuous use, to fully adhering to the treatment strategy. The committee only estimated per protocol effect for study 2 (using the parametric G-formula), given that the interpretation of the statement of task was to address the causal effect of different dosage levels (consistent with per protocol effect) rather than to start at higher or lower dosages (consistent with ITT effect). The committee only estimated ITT effect for study 3, given that the research question, which reflects the statement of task, focused on the effect of newly dispensed benzodiazepine pharmacotherapy and not long-term use for those already receiving long-term opioid therapy. See Table 3-3 for definitions of how key methodological terminology were employed in this report. Valid estimation of the per protocol requires additional adjustments for post initiation variables related to treatment switching or discontinuation. The class of analytic approaches that have been developed to adjust for post initiation variables are called "G-methods." Commonly used G-methods include inverse probability weighting (IPTW), parametric G-formula, and G-estimation (Naimi et al., 2017; Mansournia et al., 2017b).

Study Design

The design of each of the target trials was an active-comparator, new-user (Lund et al., 2015; Ray, 2003), retrospective cohort target trial emulation study (Hernán and Robins, 2016). Details on treatment strategies for each study, including defining the index start date (time zero), are described next.

Causal Assumptions

The committee reviewed the assumptions required for causal inference in the TTE approach and sought to adhere to these assumptions. The committee outlined the assumptions by Murray and colleagues (2020) and applied them in consideration of the designs of studies 1, 2, and 3. Table 3-1 reflects six key assumptions: conditional exchangeability for treatment, conditional exchangeability for adherence, conditional exchangeability for loss to follow-up/censoring, positivity, well-defined intervention, and correct model specification. The table also describes the efforts of the committee to address each assumption.

Regarding missingness in variables, the committee's approach was to consider including all variables that were important to address the research question and keep the impact of missing data minimal. Based on descriptive

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-1 Assumptions Required for Valid Causal Inference

Assumption	Explanation	Committee's Approach to Verification
Conditional Exchangeability for Treatment (ITT effect and Per Protocol effect)	A sufficient set of common causes of treatment initiation are accurately measured and incorporated into the model to control for confounding. Furthermore, analytical techniques are employed to prevent the introduction of selection bias from time-varying confounders influenced by the treatment.	Committee results were robust across various sets of confounders. The committee applied inverse probability weighting (IPTW) or parametric G-formula to address treatment-confounder feedback for treatment for per protocol effects.
Conditional Exchangeability for Adherence (Per Protocol Effect Only)	A sufficient set of common causes of adherence is accurately measured and incorporated into the model to control for confounding. Furthermore, analytical techniques are employed and designed to prevent the introduction of selection bias from time-varying confounders influenced by the treatment.	Committee results were robust across various sets of confounders. The committee applied IPTW or parametric G-formula to address treatment-confounder feedback for adherence.
Conditional Exchangeability for Loss to Follow-Up/Censoring (Per Protocol Only)	A sufficient set of common causes of loss to follow-up is accurately measured and incorporated into the model to control for confounding. Furthermore, analytical techniques are employed and designed to prevent the introduction of selection bias time-varying confounders influenced by the treatment.	Committee results were robust across various sets of confounders. The committee applied IPTW to address treatment-confounder feedback for dropout/censoring.

Positivity	All types of individuals must have the possibility of following each treatment protocol.	Verifiable by the data.
		• IPTW:
		  • Balance of baseline characteristics before and after weighting.
		  • Overlap in propensity score between treatment strategies.
		• Parametric G-formula:
		  • Examine number of veterans who followed each regimen of interest in the "real-world" data.
		  • Balance of characteristics between subsets of regimens of interest.

Well-Defined Intervention	The intervention must be sufficiently specific so the effect can be identified in the data and reproduced.	There is a well-defined and clearly specified treatment strategy and causal contrast.
Correct Model Specification	Specification of the parametric models for the inverse probability of treatment, adherence, and loss to follow-up weights and the outcome must be correct. This also includes that continuous covariates must be in the appropriate functional form, and there is sufficient flexibility in the model for the baseline hazard where applicable.	The findings were robust to a range of model specification sensitivity analyses.

SOURCE: Adapted from Murray et al., 2020.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

statistics, missing data was minimal for continuous variables (≤40 percent) and the committee used missing indicator approach for categorical variables. Due to time and resource constraints, the committee chose the missing indicator method instead of complete case analysis (which generally introduces more bias). In addition, in determining causality, the committee considered the Bradford Hill criteria, which describe a set of conditions that increase confidence that an observational relationship is causal and include coherence with existing information (biologic plausibility, consistency of the association, time sequence, specificity, strength of the association, dose–response relationship, and study design) (Strom, 2021; Hill, 1965).

Leveraging the Observed Data to Answer the Causal Question

Studies 1 and 3 report death rates (per 100,000 person-years) and hazard ratios (HRs), which compare the risk of the outcome of interest (all-cause mortality and suicide mortality) in individuals initiating treatment versus those initiating treatment in the comparator group. In study 2, mortality risk (percentage) and risk ratios are reported. One risk ratio compares the outcome of interest in individuals with higher baseline dosages to low dosage at baseline; the other compares dosage escalation strategies to those with stable dosages during the follow-up period. In addition to the unadjusted estimates, weighted and adjusted estimates (using IPTW or parametric G-formula) were calculated to adjust for potential confounding. Confidence intervals (CIs) are also calculated and reported as an indicator of the uncertainty in these estimates (more details are provided later in the chapter).

Causal Interpretation

Limitations in Application of Results in Current and Future Clinical Practice

The committee notes that the statement of task specifically mandated the study period (2007–2019) to understand the implications of opioid treatment on mortality in veterans. This is in contrast with the more typical goal of clinical research, a forward-looking endeavor aiming to provide generalizable results that will inform clinical decisions (such as receiving opioid pharmacotherapy for acute and chronic pain). Instead, the statement of task directed the committee to delve into the past, serving as a historical exposition, analyzing the implications of past practices on mortality rates and overall health. Therefore, the findings of this report are not intended by the committee to be applicable to current practices or behaviors, including those of the VHA. Because of significant changes in opioid prescribing practices both within and outside of the VHA over the past 15 years (see Chapters 1 and 2), the distinction between a goal of estimating causal effects of past practices versus informing future practices was fundamental in the committee's choices about the treatment patterns studied in the emulated trials. For example, the rapid dosage escalation strategy examined in study 2 reflected a clinical practice that is no longer common, especially given changes to clinical practice guidelines (VA/DoD, 2022, 2017).

In addition, these retrospective studies are inherently forensic, reflecting the effect of past care rather than being indicative of the mortality risks of current practices, particularly given the changes in opioid prescribing practices, the policy landscape, mental health care, and the nature of the opioid overdose epidemic in the intervening years. As reflected in the statement of task and expert perspectives, many unanswered questions remain about the causal effects of past opioid prescribing practices on mortality, especially in light of ecologic data indicating that U.S. opioid- and benzodiazepine-pharmacotherapy–related mortality has continued to climb in recent years.

In sum, the committee sought to address the statement of task in the least biased and most internally valid way, which calls on the committee to utilize best practices and recent advances in the modern causal inference literature, including TTE techniques. The committee applied this strategy to estimate causal effects of several key opioid and benzodiazepine pharmacotherapy prescribing decision points—to initiate opioid pharmacotherapy, increase opioid dosages over time, and co-prescribe opioid and benzodiazepine pharmacotherapies (Neuberger and Tallis, 1999). The committee is explicit in the causal objective, which can reduce ambiguity in the scientific question and errors in data analysis and clarify assumptions required for causal inference (Hernán, 2018). The committee adheres to best practices from the modern causal inference literature, including (1) designing the observational analysis to emulate a target trial and (2) selecting confounding adjustment variables using expert knowledge and clear articulation of the causal structure of the study question.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

STUDY POPULATION, DATA SOURCES, AND MEDICATIONS OF INTEREST

For all target trials, the study population is defined as veterans receiving care in the VHA, and the study period is from January 1, 2007, to December 31, 2019.[6] The earliest index date, or start date, was January 1, 2007. The latest possible index date was December 31, 2018, in studies 1 and 2 and October 1, 2019, in study 3. To assess exclusion and eligibility in the study and follow-up, data from 2006–2019 were pulled for analyses.

Data sources include the following:

VHA Corporate Data Warehouse (CDW): The CDW hosts data from across the VHA and includes health data, such as veteran insurance, inpatient and outpatient data, laboratory results, and prescription information (Culbreath and Gonsoulin, 2019).

United States Veterans Eligibility Trends and Statistics (USVETS): This Department of Veteran Affairs (VA) dataset includes data on U.S. veterans, such as military history, demographics, socioeconomics, and utilization of VA benefits and services, and is maintained and administered by the VA (VA, 2019).

National Death Index (NDI): This national dataset includes mortality data, from death certificates. The data include deaths from all 50 states, including Washington, DC, reflecting date and cause of death. The dataset is maintained by the National Center for Health Statistics (NCHS) (NCHS, 2024). NDI data for this project were obtained through the VA/Department of Defense Mortality Data Repository.

Centers for Medicare & Medicaid Services (CMS) Medicare Data: Through the VHA, Medicare and Medicaid Analysis Center provided access to Medicare Parts A, B, and C encounter data (which includes data on health conditions, defined by International Classification of Diseases [ICD] codes in the EHR) and Medicare Part D prescription drug events[7] (commonly referred to as "claims"). The Medicare data supplemented prescription dispensing data and other study covariates unavailable from the VA, CDW or USVETS.

The data files were linked based on the combination of a veteran's unique individual internal control number, Social Security number (SSN), and date of birth.

Westat, the subcontractor, had access to, and analyzed, the data available through the outlined sources. Only Westat had access to personally identifiable health information and personally identifiable information; all access to the data and analyses occurred within the VA firewall and data ecosystems. Final analytic aggregated results were removed from VA Informatics and Computing Infrastructure and provided to the committee only after privacy review. All approved data analysts on this study were also subject to a VA background check, maintained up-to-date human subjects training, and worked within Westat's designated workspace on the server. The National Academies of Sciences, Engineering, and Medicine (the National Academies) Institutional Review Board approved the study. Results are presented in tables and figures in each of the chapters.

Medications Included in Each Study

Medication data are from either VHA EHRs or Medicare Part D pharmacy claims data. The pharmacy data can be categorized into three measures: prescribed (prescriber submits a prescription to a pharmacy), a fill (pharmacy completes the requested prescription), and dispensed (individual picks up/is mailed the prescription from the pharmacy). In the emulated target trials, based in retrospective observational data, treatment assignments were based on the observed dispensed prescription data. It is important to distinguish the measurability of prescription dispensing data from the measurability of that ingested by the individual. A dispensed prescription does not necessarily mean that the medication was consumed, since these medications are commonly prescribed to be taken "as needed." For this study, a measure of individuals ingesting the prescription was not available in the dataset; the committee used prescription dispensing data as a proxy for medications ingested by the individual.

The committee included only systemically absorbed medications, specifically oral and sublingual medications and fentanyl patches. The committee excluded medications that are intravenously administered or are suppositories as these types are most commonly administered during end-of-life care or in inpatient settings. Additionally,

[6] Latest possible index date was December 31, 2018, in study 1 and 2 and October 1, 2019, in study 3.

[7] For the purpose of this report, the committee refers to prescription drug events as "claims" (ResDAC, 2024).

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

medications to treat seizures (nasal midazolam and rectal diazepam) were excluded; however, individuals with a diagnosis of seizures were not excluded from the study sample.

Several medications were excluded because they were either not approved for use or not available during the study period. Propoxyphene was included in the medication list of all three studies until 2010, when it was removed from the market (FDA, 2018). Paregoric, an opioid analgesic administered orally, is not approved by the Food and Drug Administration (FDA) to treat pain (Drugs.com, 2024). Valdecoxib, a non-steroidal anti-inflammatory (NSAID), was removed from the market in 2005, and zuranalone, an antidepressant, was not approved until 2023. Quetiapine, an atypical antipsychotic medication used off label for insomnia, was excluded, as it is most frequently used for mental health conditions in the VA, has known harms, and a black box warning indicating increased mortality and suicidal ideation in specific populations (VA/DoD, 2019). These exclusions were applied during pre-index, baseline, and follow up. Table 3-2 includes the full list of medications included in each study. The committee grouped medications by drug class, based on FDA or VA drug class classification. Table 3-2 shows the drug classes, corresponding medications, and role in each target trial.

Medications Identified for Treatment Strategies

In identifying medications for treatment strategies (either the treatment or comparator groups) in each study, the committee relied on clinical expertise, FDA-approved indications, VA drug classifications, and existing literature with defined comparator groups (VA, 2024; Edinoff et al., 2021a,b; Brummett et al., 2019; Deeks, 2019; LiverTox, 2019; Ali et al., 2017; Park et al., 2015; Schug and Stannard, 2011; DailyMed, n.d.). Medications included in the study were not limited to those on the CMS or VA formularies. Also, note that Medicare covered benzodiazepines beginning in 2013 (CMS, 2012). The committee included the following pharmacotherapies in the studies (for more details, see Chapters 4, 5, and 6):

- For study 1, two target trials were emulated. Study 1a focused on veterans without a current benzodiazepine pharmacotherapy, and study 1b focused on veterans with current benzodiazepine pharmacotherapy. There were two treatment strategies: The treatment group in each study included individuals newly dispensed opioid pharmacotherapy, which included full agonists and some atypical opioids (tapentadol and butorphanol) due to their widespread use in pain treatment and impact within the pain neurotransmitter route. The comparator group in each study included individuals newly dispensed non-opioid medications with a primary (e.g., NSAIDs) or secondary indication for pain: tetracyclic antidepressants (TeCA), serotonin-norepinephrine reuptake inhibitors (SNRIs), muscle relaxers, and gabapentinoids.
- For study 2, two target trials were emulated. Study 2 evaluates two prescribing strategies for individuals newly dispensed opioid pharmacotherapy (full agonist). In study 2a, veterans received varying initial dosages (low, medium, high), and in study 2b, veterans received varying dosage escalation strategies (stable, slow, and fast).
- The study 3 treatment group included benzodiazepine pharmacotherapy. The study 3 comparator group, alternative non-benzodiazepine pharmacotherapy, included medications from the VA antidepressants class (indicated for anxiety) and insomnia medications. Study 3's population of interest were those who were consistently dispensed opioid pharmacotherapy (full agonists and two atypical[8] opioid pharmacotherapy, tapentadol and butorphanol).

Medications Identified as Covariates

The committee adjusted for several medications, some of which could be confounders, to improve covariate balance between treatment and comparator groups. Specifically, acetaminophen is a covariate in all the studies. It is not included as a non-opioid analgesic comparator group in study 1 because it is not an equal comparator to

[8] Study 3's research question is focused on those consistently dispensed opioid pharmacotherapy, unlike in study 1 and study 2, which both focused on an opioid naïve population. Study 3 does not limit opioid pharmacotherapy to only full agonists.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

opioid pharmacotherapy; individuals in either the treatment (opioid pharmacotherapy) or comparator group (non-opioid pain pharmacotherapy) could be dispensed acetaminophen as well to manage pain. In addition, migraine medications are included as a covariate in all the studies rather than an exposure, because they are used to manage pain specific to the pathophysiology of migraines, not general pain. The committee notes that some medications were included in the analyses differently to reflect the study's research question. For example, in study 2, which is the only study focused on opioid dosage, the committee censored levo-alpha acetyl methadol (LAAM), buprenorphine, methadone for opioid use disorder (OUD), and naltrexone. Dosage calculations for these medications and application in the analyses were challenging given that the standard morphine milligram equivalent (MME)/day is lacking (e.g., buprenorphine and naltrexone (which is used to block effect of opioid analgesics)) and the availability of data in health records (the dose of methadone used for OUD is not recorded in VHA records). The committee adjusted for these pharmacotherapies in study 1, as they were considered possible confounders of the association between receiving opioid pharmacotherapy and mortality.

Medications Used as Exclusion Criteria

The committee excluded individuals with prescription for medications for opioid use disorder (MOUDs) at baseline because those prescribed an MOUD may not be opioid "naïve." The committee acknowledges that medication naïvety is difficult to assess; in the context of this report, the phrase "opioid naïve" refers to an individual without a dispensed prescription for opioids or MOUD in the washout period. MOUDs refer to specific formulations of methadone (including liquid and diskette formulations typically used for OUD), LAAM (used primarily for OUD), and buprenorphine (FDA formulations approved for OUD). Naltrexone, an opioid antagonist (blocks opioid receptors) used for treating OUD and other conditions, was excluded at baseline for similar reasons. In addition, buprenorphine for pain was excluded at baseline from studies 1 and 2 and butorphanol and tapentadol were excluded from study 2 at baseline because none of these medications are used as first-line treatments for pain; thus, individuals dispensed these medications would more likely not be "naïve." Individuals who are newly dispensed medications may not be new starts as this would be outside of normal clinical practice. Buprenorphine for pain was excluded at baseline from study 3 because clinicians may prescribe non-MOUD formulations of buprenorphine when a patient is known to have an OUD diagnosis or where OUD is suspected.

The committee excluded individuals with dispensed MOUD at baseline to capture those who are more likely to be opioid naïve. Additionally, the committee excluded individuals with dispensed MOUD as preliminary analyses at baseline identified that not many individuals with MOUD were receiving a simultaneous opioid prescription.

SPECIFICATIONS FOR THE EMULATED TARGET TRIALS

As mentioned, the committee employed a TTE framework to address the causal research questions. The committee specified a target trial, which is a hypothetical randomized trial, and then designed the emulated target trial using observational data. Table 3-3, which is from the 2019 National Academies report, outlines components for both the target and emulated trials. Study-specific protocols are outlined in more detail in Chapters 4 to 6. Each chapter includes a flowchart of the selection process of including eligible VHA veterans in the study.

The following section outlines each of the target trial components common across the three studies. Chapters 4, 5, and 6 provide further detail of aspects of each component specific to each study. In addition, given the complexity of each study, the committee developed a figure for each study that reflects key temporal aspects of the longitudinal study design, specifically the index or date of entry into the study, exposure washout period, windows for exclusion and covariate assessments, and follow-up time (Schneeweiss et al., 2019).

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-2 Pharmacotherapy by Drug Class Included by Study

Drug Class	Study 1	Study 2	Study 3
Opioid Full Agonist			
Benzhydrocodone	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Codeine	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Dihydrocodeine	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Fentanyl	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Hydrocodone	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Hydromorphone	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
LAAM[1] (non-liquid; for pain)	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
LAAM (non-liquid; MOUD[2])	• Included in baseline exclusion criteria • Not censored during follow-up • Confounder during follow-up	• Included in baseline exclusion criteria • Censored during follow-up	• Included in baseline exclusion criteria • Not censored during follow-up
Levomethadyl	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Levorphanol	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Meperidine (oral)	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Methadone (non-liquid/non-diskette) (for pain)	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Methadone (non-liquid/non-diskette) (MOUD)	• Included in baseline exclusion criteria • Not censored during follow-up • Confounder during follow-up	• Included in baseline exclusion criteria • Censored during follow-up	• Included in baseline exclusion criteria • Not censored during follow-up
Morphine	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Oxycodone	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Oxymorphone	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Propoxyphene	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Sufentanil (sublingual)	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest
Tramadol	Opioid pharmacotherapy (Treatment)	Opioid pharmacotherapy (Treatment)	Population of interest

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-2 Continued

Drug Class	Study 1	Study 2	Study 3
Opioid Atypical			
Buprenorphine (MOUD)	• Included in baseline exclusion criteria • Not censored during follow-up • Confounder during follow-up	• Included in baseline exclusion criteria • Censored during follow-up	• Included in baseline exclusion criteria • Not censored during follow-up
Buprenorphine (for pain)	• Included in baseline exclusion criteria • Not censored during follow-up • Confounder during follow-up	• Included in baseline exclusion criteria • Not censored during follow-up • Incorporated into morphine milligram equivalent (MME) calculations during follow-up	• Included in baseline exclusion criteria • Not censored during follow-up
Butorphanol	Opioid pharmacotherapy (Treatment)	• Included in baseline exclusion criteria • Not censored during follow-up • Incorporated into MME calculations	Population of interest
Tapentadol	Opioid pharmacotherapy (Treatment)	• Included in baseline exclusion criteria • Not censored during follow-up • Incorporated into MME calculations	Population of interest
Opioid Antagonist			
Naltrexone	• Included in baseline exclusion criteria • Not censored during follow-up • Confounder during follow-up	• Included in baseline exclusion criteria • Censored during follow-up	• Included in baseline exclusion criteria • Not censored during follow-up
Benzodiazepine			
Alprazolam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Bromazepam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Chlordiazepoxide	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-2 Continued

Drug Class	Study 1	Study 2	Study 3
Clobazam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Clonazepam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Clorazepate	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Diazepam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Estazolam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Flurazepam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Halazepam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Lorazepam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Oxazepam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Prazepam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Quazepam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Remimazolam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Temazepam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Triazolam	Stratifying medication	Confounder	Benzodiazepine pharmacotherapy (treatment)
Anti-Convulsant			
Carbamazepine	Confounder	Confounder	Confounder
Oxcarbazepine	Confounder	Confounder	Confounder
Topiramate	Confounder	Confounder	Confounder

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-2 Continued

Drug Class	Study 1	Study 2	Study 3
Antidepressants			
Amitriptyline	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Amoxapine	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Bupropion (Tab)	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Citalopram	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Clomipramine	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Desipramine	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Desvenlafaxine	Confounder	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Doxepin	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Duloxetine	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Escitalopram	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-2 Continued

Drug Class	Study 1	Study 2	Study 3
Esketamine	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Fluoxetine	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Fluvoxamine	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Impramine	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Isocarboxazid	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Levomilnacipran	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Milnacipran	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Mirtazapine	Confounder	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Nefazodone	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Nortriptyline	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-2 Continued

Drug Class	Study 1	Study 2	Study 3
Paroxetine	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Phenelzine	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Protriptyline	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Selegiline	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Sertraline	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Tranylcypromine	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Trazodone	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Trimipramine	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Venlafaxine	Confounder	Confounder	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Vilazodone	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-2 Continued

Drug Class	Study 1	Study 2	Study 3
Viloxazine	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Vortioxetine	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Antihistamine			
Hydroxyzine	Confounder	Confounder	Confounder
Anxiolytic			
Buspirone	Confounder	Confounder	Confounder
Gabapentinoids			
Gabapentin	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Pregabalin	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Insomnia			
Eszopiclone	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Ramelteon	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Suvorexant	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Zaleplon	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Zolpidem	Not included in study	Not included in study	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-2 Continued

Drug Class	Study 1	Study 2	Study 3
Migraine			
Almotriptan	Confounder	Confounder	Confounder
Aspirin w/ caffeine	Confounder	Confounder	Confounder
Eletriptan	Confounder	Confounder	Confounder
Fioricet	Confounder	Confounder	Confounder
Fioridals	Confounder	Confounder	Confounder
Fioridan	Confounder	Confounder	Confounder
Frovatriptan	Confounder	Confounder	Confounder
Naratriptan	Confounder	Confounder	Confounder
Rizatriptan	Confounder	Confounder	Confounder
Sumatriptan	Confounder	Confounder	Confounder
Sumatriptan + Naproxen	Confounder	Confounder	Confounder
ZOLMitriptan	Confounder	Confounder	Confounder
Muscle Relaxers			
Baclofen	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Carisoprodol	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Chlorzoxazone	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Cyclobenzaprine	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Dantrolene	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Metaxalone	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Methocarbamol	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Orphenadrine	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Tizanidine	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Other Non-Opioid Analgesic			
Acetaminophen	Confounder	Confounder	Confounder

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-2 Continued

Drug Class	Study 1	Study 2	Study 3
Non-Steroidal Anti-Inflammatory Drugs			
Aspirin (≥400mg)	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Celecoxib	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Diclofenac (pill)	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Diflunisal	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Etodolac	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Fenoprofen	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Flurbiprofen	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Ibuprofen	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Indomethacin	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Ketoprofem	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Ketorolac	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Meclofenamate	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Meloxicam	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Nabumetone	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Naproxen	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Oxaprozin	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-2 Continued

Drug Class	Study 1	Study 2	Study 3
Phenylbutazone	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Piroxicam	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Salsalate	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Sulindac	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Tolmetin	Non-opioid pain pharmacotherapy (opioid comparator)	Confounder	Not included in study
Serotonin-Norepinephrine Reuptake Inhibitor			
Desvenlafaxine	Confounder	Confounder[3]	Benzodiazepine comparator (non-benzodiazepine alternative)
Venlafaxine	Confounder	Confounder[3]	Benzodiazepine comparator (non-benzodiazepine alternative)
Tetracyclic Antidepressant			
Mirtazapine	Confounder	Confounder[3]	Benzodiazepine comparator (alternative non-benzodiazepine)

[1] LAAM: Levo-Alpha Acetyl Methadol.
[2] MOUD: medication for opioid use disorder.
[3] Desvenlafaxine, venlafaxine, and mirtazapine are included in study 2 in the antidepressant covariate.

continued

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TABLE 3-3 Key Components of a Target Trial Protocol

Target Trial Component	Description	Notes
Eligibility criteria	How the individual population is recruited into the target trial.	All inclusion and exclusion criteria are based on characteristics ascertained exclusively at baseline.
Treatment strategies	Each of the clinical interventions that are to be compared.	The description needs to include the initial treatment and protocol-approved reasons for discontinuation or switching.
Treatment assignment	How participants will be assigned to each treatment strategy at baseline.	The assignment is randomized, possibly conditional on baseline prognostic factors. Individuals will be aware of the treatment strategy to which they were assigned.
Outcome	Outcomes of interest and how to ascertain them.	If possible, include negative controls (i.e., outcomes that are known to be unaffected by the studied treatments).
Follow-up	Definition of when the follow-up period starts and ends for each participant.	For each eligible individual, follow-up starts at baseline (the time of treatment assignment) and ends at death, outcome, loss to follow-up, or administrative end of follow-up.
Causal contrast	What comparative effects of the treatment strategies will be estimated.	The intent-to-treat (ITT) or per protocol effect.*
Statistical analysis	How to estimate the ITT effect or per protocol effect via ITT and per protocol analyses that appropriately adjust for pre- and post-baseline prognostic factors associated with adherence and loss to follow-up.	Investigators should specify and measure the covariates potentially related to treatment choice, adherence, and outcomes at baseline and during the follow-up. Other variables that may need to be specified include those that define key subgroups.**

* ITT effect: comparative effect of assignment to the treatment strategies at baseline; per protocol effect: comparative effect of receiving the treatment strategy as specified in the protocol.

**More specifically, investigators should adjust for pre- and post-baseline prognostic factors associated with treatment and loss to follow-up.
NOTE: This table was developed by the National Academies 2019 committee and included in its report, additional clarifications have been added by the current committee.
SOURCE: NASEM, 2019.

Eligibility Criteria

For each calendar month from January 1, 2007, to December 31, 2019,[9] the committee identified eligible individuals who met the following criteria: (1) be a U.S. veteran, (2) be 18 years or older, (3) have a valid SSN, and (4) have at least 1-year continuous enrollment in the VHA between 2006–2019,[10] defined as at least one encounter in the VHA in the 12-month pre-index period. Eligible individuals also included veterans with at least one encounter in the VHA in the 12 months before index date within the eligible study period but only had a pharmacy claim through Medicare Part D (no VHA pharmacy claim). In addition, those who were eligible did not have an encounter or dispensed pharmacotherapy in Guam, Manila, or Singapore VHA facilities. These veterans were excluded given that mortality data collected in these regions are not reflected in the NDI data. See "exclusion criteria" for further information.

Eligibility Exclusion

Each study had an exclusion assessment window of 365 days before the index date. VHA veterans who received hospice or palliative care or had a cancer diagnosis (except non-melanoma skin cancer) were excluded from the study. ICD diagnosis codes from Medicare and VHA encounter data were used to identify conditions (see Appendix I for list of codes). Individuals receiving palliative care and/or in hospice were excluded, given that

[9] Latest possible index date was December 31, 2018, in study 1 and 2 and October 1, 2019, in study 3.
[10] Given that the earliest index date is January 1, 2007, the earliest pre-index data are January 1, 2006.

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having a terminal illness (and thus being eligible for these services) is related to both death and more permissive opioid prescribing and thus a confounder in the relationship between receiving opioid pharmacotherapy and death. In addition, individuals with cancer have an increased risk of mortality and often receive an opioid prescription to manage cancer-related pain. Decisions regarding opioid initiation, co-prescribing, and dosage increases may differ for cancer compared to non-cancer pain; policies and practices for opioid prescribing is (generally) more permissive for individuals with cancer (VA/DoD, 2022, 2017, 2010, 2003; Manchikanti et al., 2017; Dowell et al., 2016). Furthermore, the study exclusion criteria are in line with published studies examining opioid pharmacotherapy which excluded individuals with cancer (Song et al., 2022; Coyle et al., 2018; Berna et al., 2015; Turner and Liang, 2015; Gomes et al., 2011; Dunn et al., 2010). As a result, having cancer may be a confounder between treatment regimen and mortality; therefore, individuals with cancer, other than non-melanoma skin cancer, are excluded.

To ensure that individuals receiving MOUD treatment were excluded from the study, due to complexities to measuring MME exposure, the committee excluded any individuals who had received ≥1 dispensed MOUD formulation of LAAM, methadone, buprenorphine, or naltrexone in the 90-day pre-index period.

The committee aimed to capture all newly dispensed opioid pharmacotherapy exposure (except cancer-related and end-of-life pain, given the increased likelihood of mortality). Individuals may initially manage acute pain related to surgery, injuries, and/or other procedures using opioid or non-opioid pain pharmacotherapy and are sometimes prescribed longer-term pain pharmacotherapy (which may or may not include opioid pharmacotherapy) to manage chronic pain. Also, chronic pain often starts from an injury or experience that may be expected to result in short-term pain. Studies 1 and 3 determined that by excluding these individuals, the sample would not be generalizable to those who experience this common pathway to chronic pain. Study 2 excluded individuals with recent surgery or an acute painful injury because dosage increases are not an expected component of short-term or acute opioid prescribing.

Based on the criteria listed, each study has a figure that illustrates the selection process of veterans for the unique emulated target trial.

Treatment Strategies

The following are clinically realistic treatment strategies for each emulated target trial:

Study 1 focused on comparing the treatment group (initiating opioid pharmacotherapy) to those in the comparator group (initiating non-opioid pain pharmacotherapy). Study 1 further stratified those without and with current dispensed benzodiazepine pharmacotherapy.

Study 2 focused on comparing opioid pharmacotherapy strategies. Among veterans initiating opioid pharmacotherapy, study 2a focused on initial dosages and compared medium and high to low dosages. Study 2b focused on escalation of opioid dosages and compared slow and fast escalation to stable dosage.

Study 3 focused on comparing the treatment group (initiating benzodiazepine pharmacotherapy) to those in the comparator group (initiating alternative non-benzodiazepine pharmacotherapy for the same indications) among those consistently dispensed opioid pharmacotherapy.

Additional details on treatment strategies by study are provided in Chapters 4 (study 1), 5 (study 2), and 6 (study 3).

Treatment Assignment

In the hypothetical target trial, eligible individuals would be randomly assigned to a strategy and would be aware of their treatment assignment. In the emulated target trial, based on retrospective observational data, treatment assignments were based on the observed prescription drug events (claims) from Medicare Part D or dispensed pharmacotherapies from the VHA EHRs. Thus, the analyses considered prescription dispensing records at baseline to assign treatment group, unlike in the hypothetical target trial, for which researchers would determine the treatment assignment, which could be different from what medications ultimately are dispensed. Additional information on study-specific treatment assignment of individuals is provided in subsequent chapters.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Start and End of Follow-Up

The start date, or the index date, is when the eligible veteran was first dispensed the medication in the treatment or comparator group and all baseline eligibility criteria were met. To facilitate computation, the index date was transformed into an index month, as the analyses were conducted using aggregated monthly data. Follow-up time was 12 months[11] for studies 1 and 2 and 3 months[12] for study 3. The committee utilized all available follow-up data (through the end of 2020) with prespecified landmark analysis at 12 months. Censoring was applied to all target trials according to trial protocol. For per protocol (target trials 1 and 2), given the interest is in observing the effect of initiating and continuing the treatment strategy over a specified follow-up period, eligible individuals are followed from the time of treatment initiation (baseline) until death (or death due to other causes, in analyses of suicide mortality), cancer diagnosis (except non-melanoma skin cancer), receipt of hospice or palliative care, non-adherence to treatment (≥3 months without dispensed opioid pharmacotherapy) (not applicable to study 2), or the administrative end of follow-up (12 months in both target trials 1 and 2), whichever happens first. For ITT, eligible individuals are followed from the time of treatment initiation (baseline) until death (or death due other causes, in analyses of suicide mortality) or the administrative end of follow-up (12 months in target trials 1 and 3 months in target trial 3), whichever happens first.

Outcomes

The outcomes outlined in the statement of task are all-cause mortality and suicide mortality, which were identified through linked data from the NDI. The committee determined all-cause mortality as the primary outcome and suicide mortality as the secondary outcome. Suicide mortality was identified by the ICD-10 death codes X60-X84 (intentional self-harm), U03 (intentional self-harm (suicide)), and Y87.0 (sequelae of intentional self-harm) (Hirsch et al., 2016; CDC, 2002). The period of outcome measurement varied based on the length of follow-up for each study. The terms "primary" and "secondary" are those most commonly employed by epidemiological studies and do not reflect hierarchy of importance.

Causal Contrast: Intent-to-Treat and Per Protocol Effects

For study 1, both per protocol (main) and ITT (secondary) effects were estimated. For study 2, per protocol effect was estimated. For study 3, ITT effect was estimated.

Study Design

The design of all studies was an active-comparator, new-user (Lund et al., 2015; Ray, 2003), retrospective cohort target trial emulation study (Hernán and Robins, 2016).

Covariates

To strengthen causal inferences, the committee controlled for many covariates to adjust for baseline and/or time-varying confounding and achieve balance between the treatment and comparator groups.

- Sociodemographics,
- Health conditions and behaviors,
- Supplemental health insurance to VHA coverage,
- Health care utilization,

[11] The committee selected 12 months of follow-up for studies 1 and 2 to provide longer length of follow-up than other initiation studies (Larochelle et al., 2022), yet sufficient length to reduce non-adherence.

[12] The committee selected a 3-month follow-up for study 3 to capture the acute effect of concomitantly dispensed opioid and benzodiazepine pharmacotherapy on mortality.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

- Specific pharmacotherapies,
- Facility,
- Facility-level characteristic, and
- Calendar month of eligible dispensed pharmacotherapy.

Additional covariates include month and the interaction of state and year as fixed effects. Baseline covariates included demographic characteristics (e.g., age, sex, race/ethnicity, marital status, disability status), supplemental insurance to VHA coverage (i.e., Medicare, TRICARE, or private insurance), housing security (e.g., history of homelessness status), physical and mental health conditions/disorders (e.g., acute painful injury, anxiety, chronic obstructive pulmonary disease, cardiovascular disease, substance use disorders, diabetes), military status (e.g., service era, military branch, combat service), body mass index, health care utilization in prior year (e.g., VHA outpatient visits, inpatient hospital admissions, nursing home stay), VHA facility-level characteristic (e.g., urbanicity), and specific pharmacotherapies that the committee considered as potential confounders (which varied for each study, such as migraine medications, anxiolytics, and anticonvulsants; see Table 3–3 for the detailed medication list). The committee evaluated candidate variables readily available in the study clinical and administrative databases. See Appendix I for a list of all health conditions and corresponding ICD codes.

The studies did not require participants to have a chronic pain diagnosis in the primary analysis. Studies have shown that individuals identified with chronic pain did not have a pain diagnosis or pain was underreported in electronic medical records compared to pain reported in a patient-based survey (Frank et al., 2019; Goulet et al., 2016).

Lastly, based on a priori hypotheses that effects may vary by specific individual subgroups, the committee identified a subset of variables to be evaluated for effect modification (see the "Subgroup Analyses" section) (Suda et al., 2023; Gellad et al., 2018).

Time-Varying Covariates

In studies 1 and 2, pain intensity, which is measured by the average of all documented pain intensity ratings[13] (also referred to as "pain scores") within a month in the VA EHR, was considered as a time-varying covariate. The measure was updated monthly in the dataset and incorporated in the IPTW. When a new measurement was unavailable, the last observation was carried forward indefinitely until a new measurement was available or the individual was censored. In study 2, pain score and benzodiazepine prescription are time-varying covariates. Preliminary analyses demonstrated that most individuals in the study had 1 pain score. Those who had multiple pain scores were typically hospitalized for some time during the month. Both the exposure (average daily opioid dosage) and this variable were measured over month periods. Study 3 does not include any time-varying covariates.

Accounting for Secular Trends and Variation by Facility

Facility and calendar time (12 months) were captured as fixed effects to capture facility-specific variation (e.g., clustering of individuals within a facility, geographic variation by facility) and reflect changes over time (e.g., variation in behaviors (health care seeking, prescribing)) and prevalence of conditions during a year. The committee also included the interaction term (i.e., product term) between state and year to capture variation over time and by states, such as when state or facility policies related to opioid prescription were implemented (e.g., when states began to participate in the Prescription Drug Monitoring Program) or secular trends in state-level policies and intensities during the opioid epidemic.

[13] Current pain intensity ratings were based on the numeric rating score survey, with 0 = no pain to 10 = worst pain imaginable, obtained during clinical encounters.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Statistical Analysis

The causal effects of target trials were either per protocol effect (studies 1 and 2) or ITT effect (studies 1 and 3). Studies 1 and 3 estimated the effects using an unadjusted and adjusted (IPTW) pooled logistic regression model. In study 2, per protocol effect was estimated using parametric G-formula. All analyses were conducted using SAS 9.4 and SAS Enterprise Guide (Logan et al., 2022). Study results do not report data if sample sizes were 10 or fewer individuals. This helps to ensure confidentiality of individuals in the study and is in line with CMS data policy and NCHS recommendations (NCHS, 2023; HHS, 2020). Furthermore, cells are marked as unreliable where sample sizes were 20 or fewer (NCHS, 2023).

Accounting for Baseline Differences: Inverse Probability Treatment Weights

To account for the baseline difference between treatment and comparator groups in each target trial, analyses were weighted using IPTW for studies 1 and 3. IPTW is a method used to adjust for covariates and potential confounding in observational studies that uses a function of the propensity score (PS) of receiving treatment based on individual factors. By weighting each individual included in the analysis by the inverse of the probability of receiving the treatment or comparator treatment helps achieve balance between the treatment and comparator groups (Xu et al., 2010; Robins, 1986).

To calculate the IPTW,[14] first the committee performed a logistic regression to calculate the PS, or the likelihood of being the treatment versus comparator group. The PS was modeled by fitting a logistic regression of the medication received (treatment versus control) as a function of the covariates described above. For per protocol analysis, IPTW was a function of both baseline and time-varying covariates; for ITT analysis, the IPTW was a function of only the baseline covariates (Robins et al., 2000). Second, the IPTW was calculated using the inverse of the PS, or 1/PS, for those in the treatment group and 1/(1-PS) for those in the comparator group.

To limit the influence of extreme weights on the results, the committee winsorized weights to the middle 98 percent by applying the first percentile weight to all observations below the first percentile and the 99th percentile weight to all observations above the 99th percentile. The distribution of the propensity scores by treatment group was depicted using histograms. In addition, the balance of baseline covariates between the two groups before and after IPTW was assessed using the absolute standardized mean difference (ASMD). An ASMD of ≤0.1 between the two groups after weighting suggests reduction of imbalance between the group due to bias (Austin, 2009). Missing values were handled using the missing covariate indicator methods, which assigned a missing category in the model (e.g., Hispanic ethnicity, non-Hispanic ethnicity, missing ethnicity).

Study 2 uses an alternative method, the parametric G-formula, given the sustained treatment strategies of interest (more detail described below and in Chapter 5) which uses an extension of the standardization approach to ensure balance of covariates between treatment strategies. Under this method, outcomes are estimated as if the entire sample had received a given treatment regimen. This process is repeated for each treatment regimen. Thus, the covariates of individuals are balanced and reflect the underlying distribution of covariates in the eligible individual population.

Per Protocol Effect

The per protocol effect corresponds to the effect of adhering to the assigned treatment strategy over the follow-up. In per protocol analysis, the committee required individuals, regardless of treatment strategy group, to consistently follow the treatment protocol. Individuals were censored if they stopped following the study's treatment protocol. To account for the baseline difference between veterans of differing treatment strategies, per protocol

[14] More detail in calculating the IPTW for per protocol (only study 1): To adjust for risk factors associated with treatment initiation (or adherence), time-varying non-stabilized inverse-probability weights are estimated via a pooled logistic regression model for the monthly probability of treatment that includes baseline (ITT and per protocol effect) and time-varying factors (per protocol effect). The following weights were calculated: (1) a baseline treatment weight to adjust for measured confounding in the likelihood of initiating the treatment versus comparator group (i.e., the IPTW described above); (2) an adherence weight (monthly); and (3) a censoring weight for loss to follow-up (monthly).

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

analyses were weighted using IPTWs (not applicable to study 2). In the per protocol analysis, the pooled logistic regression was fit after censoring individuals if, and when, they deviated from their initial treatment strategy using the time-dependent medication follow-up variable. In study 1, the per protocol model was adjusted for baseline covariates (same as in ITT), time-varying variables, and adherence to treatment protocol.

Intent-to-Treat Effect

The ITT effect corresponds to the effect of being assigned to a treatment strategy (e.g., initiating opioid versus non-opioid pain pharmacotherapies at baseline) on mortality, irrespective of subsequent cross-over or treatment discontinuation occurring during follow-up. In the ITT analysis, the committee estimated HRs, risk ratios, mortality rate, mortality risk) of death for each treatment strategy using pooled logistic regression models. In the ITT model, assuming a low monthly risk of death, an HR measured the risk of all-cause and suicide mortality between treatment strategies.

Parametric G-formula

The parametric G-formula is an innovative causal inference analytic approach to estimate effects of sustained treatment strategies. This is useful for studying interventions that are defined as a course of a stable treatment for a certain length of time or one that changes under specific conditions (i.e., a dynamic treatment strategy). A common issue with studying sustained treatment strategies is the problem of misalignment of time anchors. Parametric G-formula methods overcome this via simulation. Compared to traditional observational study methods, the parametric G-formula also can appropriately adjust for treatment-confounder feedback. The parametric G-formula is a three-step process: (1) generate prediction models using regression for all time-varying covariates used in the study and the outcome, (2) conduct Monte Carlo simulation to iteratively estimate the outcome at each follow-up time if all individuals in the sample received a specific treatment strategy (repeated for each strategy), and (3) use bootstrapping (repeat steps 1 and 2) to generate 95 percent CIs for the estimates. The committee identified a minimum of 399 bootstraps as sufficient (Davidson and MacKinnon, 2001).

Additional Analyses

Subgroup Analysis. Subgroup analyses were conducted by age (with two categorical comparisons: 18–64 versus ≥65 and 18–34, 35–54, 55–74, ≥75), race (White, Black, Native American/Alaskan Native, Asian, Hawaiian and Pacific Islander, more than one race, and missing), ethnicity (Hispanic and non-Hispanic), sex (male and female), time period (2007–2012 versus 2014–2019), and by payment source of dispensed medications (only Medicare Part D prescription claims, only VHA prescription claims, or both during the episode). The committee selected these subgroups to examine differences given older age groups, specific racial and ethnic groups, and males have been shown to be at increased risk for mortality (Bohnert and Ilgen, 2019; Bossarte et al., 2012). In addition, age categories used in the reports on veteran suicides were included in the subgroup analysis for consistency (VA, 2018).

The committee included time period as a subgroup to examine temporal changes in mortality risk. The committee selected before or after 2013, given the introduction of the VHA's Opioid Safety Initiative that year. The committee stratified by payment sources of dispensed pharmacotherapies during an episode: Individuals were grouped as having prescriptions dispensed from only the VHA, only Medicare Part D, or both. Payment source of dispensed medication is a proxy for care, access, and coordination. Other research examining payment source suggest that multiple sources of payment are associated with risky opioid prescribing, such as concurrent prescribing of opioids and benzodiazepines and prescribing with a high MME/day for opioid pharmacotherapy (Becker et al., 2017).

In addition, for studies 1 and 3, the committee repeated the main analysis for those with and without a recent surgery or outpatient procedure. Studies 1 and 3 included veterans with acute painful injury or inpatient/outpatient surgery/procedures because (1) the committee aimed to focus on pain itself, (2) treating acute pain can

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

result in overdose or OUD, and (3) these individuals may initially manage acute pain related to surgery and/or other procedures using short-term opioid pharmacotherapy and be eventually prescribed opioid pharmacotherapy to manage chronic pain.

Sensitivity Analysis. Study 3 conducted two sensitivity analyses to examine the impact of (1) increasing from >1 to >5 tablets and (2) extending the follow-up period from 3 to 12 months.

Table 3-4 lists terms used throughout the report.

LIMITATIONS

The committee acknowledges several limitations to consider in emulating the target trials in the studies, especially for the exposure/treatment of interest, outcome of interest, and methods applied. Additional study-specific limitations are included in Chapters 4, 5, and 6.

Generalizability of Results

The focus of this report was on veterans receiving care from the VHA, in keeping with the statement of task. Given their unique characteristics, caution should be taken in generalizing these findings to non-VHA veterans and non-veteran populations.

Measuring Exposure

Other sources of the treatment of interest were not available to the committee. For example, the committee did not have access to data on other sources of opioids (e.g., opioids used outside of the therapeutic setting), past exposure to prescription opioid pharmacotherapy, such as during active duty or through coverage from other payers and by payer type (e.g., commercial, TRICARE, self-pay), and over-the-counter use of medications such as NSAIDs or acetaminophen. Furthermore, methadone administered through methadone clinics (opioid treatment programs) may not be fully captured. Additionally, a measure of whether multiple medications were ingested together or separately was not captured; the proxy used is co-occurring dispensed pharmacotherapies.

Another limitation is accurately capturing an active-comparator design. For example, although tricyclic antidepressants (TCAs), SNRIs, and gabapentin are common adjuvants for pain management and included as comparators in study 1, they are also used for other indications, such as anxiety and depression. In addition, per the statement of task, the study did not assess non-pharmacotherapies that individuals may have used to help manage pain prior to study enrollment. Notably, nonpharmacologic treatments for pain (e.g., physical therapy, acupuncture, or chiropractic care) are included in VA benefits and have been increasing in utilization in recent years.

Pharmacotherapies in each active comparator group (study 1: non-opioid pain pharmacotherapy; study 3: alternative non-benzodiazepine pharmacotherapy) have potential for confounding by indication. A perfect active comparator to opioid pharmacotherapy in terms of their efficacy in nociceptive pain reduction and safety risks does not exist. TCAs, SNRIs, muscle relaxants, and gabapentinoids are indeed options for chronic pain management—including neuropathic, nociceptive, and other types of pain—but the committee acknowledges that they differ from opioids in their efficacy and safety profiles. The committee's rationale for selecting these medications as active-comparators stems from their common use in treating various forms of chronic pain. While they are not identical to opioids in terms of efficacy and safety, the committee believes that comparing individuals dispensed opioid pharmacotherapy to those dispensed non-opioid pain pharmacotherapy provides a less biased approach than comparing those newly dispensed opioid pharmacotherapy to those not newly dispensed an opioid pharmacotherapy, which could introduce greater confounding. The committee conceptualized the active comparator to benzodiazepine pharmacotherapy in study 3 similarly.

Opioid dosage was measured based on MMEs; the MME is ideal to measure the intensity of opioid exposure, as it standardizes opioid prescriptions, considering differences in the potency, quantity, and strength of different

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TABLE 3-4 Key Methodological Terms: National Academies VA Opioids Study

Methodological Terminology	Definitions
Active-comparator, New-user Design	Study design that emulates the intervention part of a randomized controlled trial trial by creating cohorts of individuals who were newly prescribed a medication and comparable to individuals who were newly prescribed an alternate treatment and following them over time for outcomes of interest (Lund et al., 2015).
Day 0	The first date an individual can qualify for the study and matches the index date (e.g., January 1, 2007).
Dosage	Total prescribed MME/per day of opioids.
Dose	Specific MME quantity in a unique tablet, patch, or capsule of opioids.
Dispensed	Status in which a prescription has been both released by the pharmacy and picked up by the individual.
Episode	The time frame beginning at the point at which a VHA veteran meets inclusion criteria through all continuous months until study end or point of exclusion (as defined in study protocol).
G-Formula	Analytic approach to estimate effects of sustained treatment strategies. It involves three steps: regression, simulation, and effect estimation.
Index Date	The date when eligibility is determined, treatment is identified, and follow-up period starts. It can occur at any point during the study period.
Intent-to-Treat Analysis	Analysis that estimates the effect of assignment to a treatment strategy (Dickerman et al., 2019).
Inverse Probability of Treatment Weighting	Statistical method used to adjust for covariates and potential confounding in observational studies that uses a function of the propensity score (PS) of receiving treatment based on individual factors. By weighting each individual included in the analysis by the inverse of the probability of receiving the treatment or comparator treatment helps achieve balance between the treatment and comparator groups (Xu et al., 2010; Robins, 1986).
Landmark Analysis	An observational method used in clinical research to "correct for the bias inherent in the analysis of time-to-event outcome between groups determined during study follow-up.… In the landmark method, a fixed time after the initiation of therapy is selected as a landmark for conducting the analysis of survival by response" (Dafni, 2011).
Naïve	The committee defined "opioid naïve" as an individual without a dispensed prescription for opioids or MOUD in the washout period (Lee et al., 2023).
Newly Dispensed	The committee notes differences in types of pharmacy data measures. Pharmacy data can be categorized into three measures: *prescribed* (prescriber submits a prescription to a pharmacy), *filled* (pharmacy completes the requested prescription), and *dispensed* (individual picks up/is mailed the prescription from the pharmacy). The committee used dispensed pharmacy data in its analyses. The committee operationalized the term "initiation" in the statement of task as "newly dispensed" pharmacotherapy in analyses. "Newly dispensed" was defined as pharmacotherapy of interest not previously dispensed (or initiation of pharmacotherapy) to the individual in the 90 days prior to the start date.
Per Protocol Analysis	Analysis that estimates the effect of adherence to an assigned treatment strategy (Smith et al., 2021; Hernán and Robins, 2017).
Pragmatic Trial	Approach that evaluates the effectiveness of a treatment under real-world conditions (e.g., no blinding, placebo controls).
Retrospective Cohort Study	Study designs in which cohorts are historically identified and compared over time. Individuals in the cohorts may have already developed the outcomes of interest prior to study initiation (Capili and Anastasi, 2021).
Right Censoring	In a study with accumulating follow-up observation time, censoring occurs when an individual ceases to continue under observation.

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 3-4 Continued

Methodological Terminology	Definitions
Target Trial Emulation	"Target trial emulation is the application of design principles from randomized trials to the analysis of observational data, thereby explicitly tying the analysis to the trial it is emulating. The purpose is to improve the quality of observational epidemiology through the application of trial design principles, even when, or perhaps especially when, a comparator trial is not yet available or feasible" (Labrecque and Swanson, 2017).
Target Trial Framework	"The target trial framework provides an organizing principle for the design of observational studies that leads to clinically interpretable results and analytic approaches that can prevent common biases. Explicitly documenting the target trial that can be emulated in available observational data provides a base for in-depth discussion between experts to decide what is and is not acceptable in relation to study design. It also provides a link between observational studies and randomized trials, so the design quality of all studies that ask questions about the effectiveness and safety of medical treatments can be judged symmetrically" (Matthews et al., 2023).
Treatment Strategy	The treatment regimen assigned to an eligible individual. (e.g., treatment strategy 1: dispensed opioid pharmacotherapy versus treatment 2: dispensed non-opioid pain pharmacotherapy).
Washout Period	"A washout period is defined as a time between treatment periods that is intended to prevent mis-interpreting observations about study-related treatments that were actually due to prior therapies" (Harvey et al., 2021).

NOTES: MME = morphine milligram equivalents; VA = Department of Veterans Affairs.

types of dispensed opioid pharmacotherapy. The committee calculated MMEs using conversions from the Centers for Disease Control and Prevention (Dowell et al., 2022).

For benzodiazepine pharmacotherapy, the committee examined other conversion methods but did not identify one as standard as the MME conversion for opioid medications. In addition, no standard definition of low, moderate, or high doses exists. Thus, comparing presence or absence of different dosages of benzodiazepine pharmacotherapies, while not ideal, was the best method available. Alternative non-benzodiazepine pharmacotherapy has the same issues (lack of a standard conversion and definition of low to high dosage). Similar to opioid pharmacotherapy, the committee did not examine historical or non-therapeutic use of benzodiazepine pharmacotherapy and/or those paid for through other sources (e.g., TRICARE, private payer). Per the statement of task, the study did not assess non-pharmacologic therapies to manage anxiety, sleep, or other indications for which benzodiazepine pharmacotherapy may be prescribed. Many veterans are at increased risk for adverse events (e.g., gastrointestinal bleeds, renal/liver dysfunction) from non-opioid pain pharmacotherapy (Kovac et al., 2010). Individuals who are at higher risk of NSAID-related adverse events likely have a higher propensity for being prescribed opioid pharmacotherapy as an alternative to NSAIDs, therefore potentially increasing risk for mortality or opioid-related adverse events.

Measuring Suicide Mortality

There are challenges in distinguishing between unintentional and intentional injury deaths. In general, cause of death of individuals may be classified as intentional (self-inflicted, or suicide) or unintentional. However, some individuals who died by suicide may have been inaccurately recorded as an unintentional death or vice versa—some individuals who died by an unintentional death are recorded as a suicide. In addition, the intent of some deaths remains unknown. Lastly, the committee did not include in the analysis history of suicide attempt or overdose.

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Variation in Prescribing Practices

Over the last two decades, the VHA continues to promote reducing high-risk prescribing of opioid pharmacotherapy for pain. However, variation exists across providers and facilities in behaviors related to reducing high-risk opioid prescribing practices, including clinical practice based on the most recent updated clinical guidelines. This variation impacts the ability to capture the practice of these risk mitigation strategies and control for them in the analyses.

An observed increased risk of exposure to multi-source opioid medications or co-prescribing across the study period could be due to care coordination, increased "access" to opioid pharmacotherapy (by non-VHA and VHA providers), less evidenced-based care generally provided in the private sector, and VHA's implementation of opioid risk mitigation initiatives before the private sector. Variation in prescribing practices by provider and time were captured by including facility, state, month, and year, and year in the analyses.

Potential Underreporting and Inaccuracies in Health Record Data

Despite the advantages in using data from health records, limitations exist in leveraging real-world data to generate evidence that be applied in clinical practice; however, unmeasured confounding may still remain. One concern is the reliability of data documented in structured data fields in EHRs, including diagnostic codes and similar clinical data, which could be measured with validated algorithms. The committee was unable to adjust for misdiagnoses or inaccuracies in clinical data reporting or distinguish between varying severity of conditions.

Although a comprehensive approach was employed to identify and adjust for known variables that could influence prescribing, a range of provider and individual-level factors remained unmeasurable from the structured components of medical records. Examples included provider decision to prescribe individual socioeconomic status such as income, education, employment; other sources of opioid or benzodiazepine pharmacotherapy; travel distance to the VHA facility; and insurance type other than VHA or Medicare. These factors could influence prescribing of opioid or other non-opioid pain pharmacotherapies or recommendation of an alternative pain management approaches. The same is true for decisions regarding prescribing benzodiazepine and alternative non-benzodiazepine pharmacotherapies. Differences in factors that influence prescriptions used in the treatment versus the comparator groups are only partially addressed by the analytic approaches employed.

Furthermore, veterans receiving care in the VHA are widely known to have higher rates of co-occurring medical and mental health disorders, and it is not uncommon for them to be prescribed multiple medications, including psychotropic medications that may negatively interact with opioid and benzodiazepine pharmacotherapies. Although the committee adjusted for multiple physical and mental health disorders, the committee was unable to adjust for unmeasured instances of polypharmacy that may interact with opioids and benzodiazepine pharmacotherapies. Concerns about polypharmacy and potentially inappropriate medications among veterans in the treatment and comparator groups are only partially addressed by the analytic approaches employed.

Despite excluding or censoring veterans receiving MOUD, this analysis likely retained veterans with untreated OUD, who may have an increased risk of overdoses, including those that are fatal. This may contribute to overestimation of mortality risks. Additionally, it is possible that veterans had an end-of-life diagnosis but had not yet received palliative care services or been placed in hospice. As a result, some veterans included in the analysis may have had opioid treatment patterns reflective of practices where the need for end-of-life pain management outweighed any risk of an opioid-related adverse event. In addition, uptake of palliative care and hospice increased over the study period.

Additional and specific limitations are reflected in the study-specific chapters.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

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4

The Effect of Opioid Prescription on All-Cause Mortality, Including Suicide Mortality, Among Those Without and With Current Benzodiazepine Prescription

INTRODUCTION

This chapter examines the effect on all-cause mortality and suicide mortality of the prescribing of opioid pharmacotherapy versus non-opioid pain pharmacotherapy among veterans without or with concomitant benzodiazepine pharmacotherapy who received care from the Veterans Health Administration (VHA). The subsequent two chapters will also examine all-cause mortality and suicide mortality and compare the effect of different initial opioid pharmacotherapy dosages and opioid dosage escalation treatment (Chapter 5) and VHA veterans on long-term opioid therapy pharmacotherapy, the effect of those newly dispensed benzodiazepine pharmacotherapy versus those newly dispensed alternative non-benzodiazepine pharmacotherapy used to treat anxiety and other common indications (Chapter 6).

Use of Opioid Pharmacotherapy to Treat Pain

Pain represents a significant public health challenge with an even more pronounced impact on U.S. veterans due to the substantial risk of pain because of military training and combat-related injuries and other occupational hazards complicated by related traumatic brain injury, posttraumatic stress disorder (PTSD), and other mental health and substance use disorders (Yang et al., 2022; Howard et al., 2022; Buttner et al., 2017; NASEM, 2013; Larson et al., 2012; Hoge et al., 2004). Since the 1990s, the use and promotion of prescribed opioid pharmacotherapy to relieve pain has been associated with increases in opioid use disorder (OUD), dependency, overdose, suicide, and overall mortality (Sandbrink et al., 2023; Moore et al., 2023; Bohnert and Ilgen, 2019; Chou et al., 2015; Bohnert et al., 2011).

Although research on the long-term efficacy of opioid pharmacotherapy on chronic pain is limited, evidence increasingly indicates the association of sustained opioid pharmacotherapy use with OUD and increased overall mortality in the general U.S. population, including veterans. Further complicating the issue is the co-prescribing rate of benzodiazepine pharmacotherapy, as the concurrent use of opioid and benzodiazepine pharmacotherapy increases the risk of unintentional overdose and suicide.[1] Despite the known risks (see Chapter 1), alternatives to opioid pharmacotherapy for significant chronic pain are limited, leading to their continued prescription.

[1] The VA has explicit guidelines advising against the prescribing benzodiazepine pharmacotherapy for treatment of PTSD among veterans due to mounting evidence of harms associated with chronic benzodiazepine pharmacotherapy prescribing in patients with PTSD and a demonstrated lack of benefits from their prescribing for the treatment of PTSD symptoms. See the VA/DoD 2017 Practice Guideline for the Management of PTSD for further information (VA, 2022).

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

To address the opioid crisis, the Department of Veterans Affairs (VA) and the Department of Defense (DoD) introduced the Clinical Practice Guidelines (CPGs) for Opioid Therapy for Chronic Pain in 2003 with updates in 2010, 2017, and 2022 (VA/DoD 2022, 2017, 2010, 2003). In a parallel effort, the VA launched the Opioid Safety Initiative (OSI) in 2013, leading to a substantial reduction in opioid prescriptions from 2013 to 2018 (Dieujuste et al., 2020) (see Chapter 2 and Appendix D for an in-depth exploration of the policy landscape surrounding the opioid crises at this time). However, prescription opioid pharmacotherapy continues to be a treatment modality to manage pain in the United States (CDC, 2023; Jones et al., 2018; Pergolizzi et al., 2018; Rosenblum et al., 2008).

In response to growing concerns regarding opioid pharmacotherapy use and the concurrent use of opioid and benzodiazepine pharmacotherapies among veterans between 2007 and 2019, Congress sought an evaluation from the National Academies of Sciences, Engineering, and Medicine (National Academies) and required the National Academies to "evaluate the effects of opioid and benzodiazepine use on all-cause mortality of U.S. veterans, including suicide mortality, regardless of whether information relating to such deaths has been reported to the U.S. Centers for Disease Control and Prevention (CDC)". Specifically, the committee will quantify the effects of opioid and benzodiazepine prescribing on the risk of death among veterans who received care from the VHA between 2007 and 2019. In the analysis presented in this chapter, the committee focuses on parts (a) and (d) of the statement of task:[2]

> "(a) the effect of opioid prescribing for pain, relative to alternative non-opioid pain treatments,"
> and
> "(d) the effect of initiating opioids among patients already taking benzodiazepines."

To address the statement of task, the committee used VHA data available from 2007 to 2019, Centers for Medicare & Medicaid Services (CMS), and National Death Index (NDI) data and modern causal inference methods to estimate the per protocol effect of initiating and continuing opioid pharmacotherapy versus non-opioid pain pharmacotherapy on all-cause mortality and suicide mortality among those with and without currently dispensed benzodiazepine pharmacotherapy. To strengthen the inferences based on the results, the committee's approach aligns with current best practices in causal inference, including utilizing target trial emulation techniques, the comparison of clinically realistic treatment strategies, the avoidance of biases related to mishandling time zero, and adjustment for baseline and time-varying confounding.

STUDY 1 METHODS

Study 1 aimed to answer the following causal research question: Among veterans receiving care in the VHA who were not consistently[3] dispensed[4] pain pharmacotherapy between 2007 and 2019, what is the effect of newly dispensed[5] opioid versus non-opioid pain pharmacotherapy on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) among those without and with current use of benzodiazepine pharmacotherapy within a 12-month follow-up period?

The committee designed this observational analysis to emulate a target trial of per protocol (main) and intent-to-treat (secondary) analysis. The target trial is the hypothetical randomized pragmatic trial that would have best answered the causal question. Target trial emulation (TTE) framework has two steps: (1) specify the protocol of the target trial, and (2) specify how the target trial will be emulated using observational data. TTE framework is useful because it helps to ensure comparison of realistic treatment strategies, avoids biases from misalignment of

[2] Parts (b) and (c) of the statement task are addressed in Chapters 4 and 5 of this report.

[3] Not dispensed any qualifying opioid or non-opioid pain pharmacotherapy in the 90-day pre-index period.

[4] The committee notes differences in types of pharmacy data measures. Pharmacy data can be categorized into three measures: *prescribed* (prescriber submits a prescription to a pharmacy), *filled* (pharmacy completes the requested prescription), and *dispensed* (individual picks up/is mailed the prescription from the pharmacy). The committee used dispensed pharmacy data in its analyses.

[5] The committee operationalized the term "initiation" in the statement of task as "newly dispensed" pharmacotherapy in analyses. In the committee's studies, "newly dispensed" was defined as pharmacotherapy of interest not previously dispensed (or initiation of pharmacotherapy) to the individual in the 90 days prior to the start date.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

time anchors (time zero/index date), and uses enhanced statistical techniques for minimizing confounding (Hernán and Robins, 2016; Gomes et al., 2022).

The protocol and specifications of the target trial (study 1) and how the committee emulated the target trial in the observational data are described in the following subsection and summarized in Table 4-1.

TABLE 4-1 Specifications for Study 1 Target Trial Protocol

Protocol Component	Target Trial Specification	Target Trial Emulation
Eligibility Criteria	• U.S. veteran • Age ≥18 years • Valid Social Security number • At least one encounter in Veterans Health Administration during 2007–2019 Exclusion: • ≥1 encounter or dispensed pharmacotherapy in Guam, Manila, Singapore Department of Veterans Affairs facilities • Hospice or palliative care within past 12 months of index date • Cancer diagnosis (except non-melanoma skin cancer) within past 12 months of index date • ≥1 dispensed medications for opioid use disorder (MOUD)[1] in 90-day pre-index • Any dispensed qualifying opioid pharmacotherapy in the 90-day pre-index period • Any dispensed qualifying non-opioid pain pharmacotherapy in the 90 days pre-index period • First eligible dispensed pharmacotherapy after January 1, 2019 Baseline is defined at the first month in which all eligibility criteria are met. Eligible individuals were either in one of two trials: • Trial 1a: without current benzodiazepine dispensed pharmacotherapy: <5 tablets of benzodiazepine pharmacotherapy within 90 days before the index date or • Trial 1b with current benzodiazepine dispensed pharmacotherapy: ≥5 tablets of benzodiazepine pharmacotherapy within 90 days before the index date	Same as target trial
Treatment Strategies	Each individual is assigned to one of the following treatment strategies, initiated at baseline and continued over follow-up: 1. Initiate non-opioid pain pharmacotherapy at baseline and continue over follow-up 2. Initiate opioid pharmacotherapy at baseline and continue over follow-up *Note: Under both strategies, individuals need to be dispensed ≥7-day supply of the relevant therapies*	Same as target trial Defined the date of initiation to be the first date of a dispensed pharmacotherapy

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-1 Continued

Protocol Component	Target Trial Specification	Target Trial Emulation
Treatment Assignment	Individuals are randomly assigned to a strategy at baseline and are aware of their assigned strategy.	Assumed randomized conditional on baseline covariates (sociodemographics, health conditions and behaviors, supplemental health insurance to VHA coverage, health care utilization, specific pharmacotherapies, facility, facility-level characteristic, and date of eligible dispensed pharmacotherapy (calendar month)).
Outcomes	Primary: All-cause mortality Secondary: Suicide mortality	Same as target trial (both based on National Death Index data and International Classification of Disease codes)
Start and End of Follow-Up	For each individual, follow-up starts at strategy assignment or treatment initiation (baseline). For per protocol analysis, eligible individuals are followed until all-cause and suicide mortality, non-adherence to treatment (≥3 months without dispensed opioid pharmacotherapy), cancer diagnosis (except non-melanoma skin cancer), receipt of hospice or palliative care during follow-up, or administrative end of follow-up at 12 months, whichever occurs first. For intent-to-treat (ITT), eligible individuals are followed until death (or death due to other causes, in analyses of suicide mortality), or administrative end of follow-up at 12 months, whichever occurs first.	Same as target trial
Causal Contrast	Primary: Per protocol effect Secondary: ITT effect	Primary: Observational analogue of per protocol effect Secondary: Observational analogue of ITT effect
Statistical Analysis	Primary: Per protocol analysis using inverse probability treatment weights (IPTW). Censor participants when deviate from assigned treatment strategy. Secondary: ITT analysis using IPTW Subgroup analysis by age, sex, race, ethnicity, payment source for dispensed pharmacotherapy, time period, surgical procedures). Estimated with the per protocol approach, as this is the main analysis.	Observational analogue of ITT effect and per protocol effect. Same subgroup analyses

[1] MOUD formulation of buprenorphine, methadone, LAAM, or naltrexone.

In addition, given the complexity of each study, the committee developed Figure 4-1, which reflects key temporal aspects of the longitudinal study design, specifically the index or date of entry into the study, exposure washout period, windows for exclusion and covariate assessments, and follow-up time (Schneeweiss et al., 2019).

Study Population and Data Sources

The study population is defined as veterans receiving care in the VHA, and the study period is from January 1, 2007, to December 31, 2019. The earliest index date, or start date, was January 1, 2007.[6] The latest possible index date was December 31, 2018. To assess exclusion and eligibility in the study and follow-up, data from 2006–2019 were pulled for analyses.

[6] Given that the earliest index date is January 1, 2007, the earliest pre-index date is January 1, 2006.

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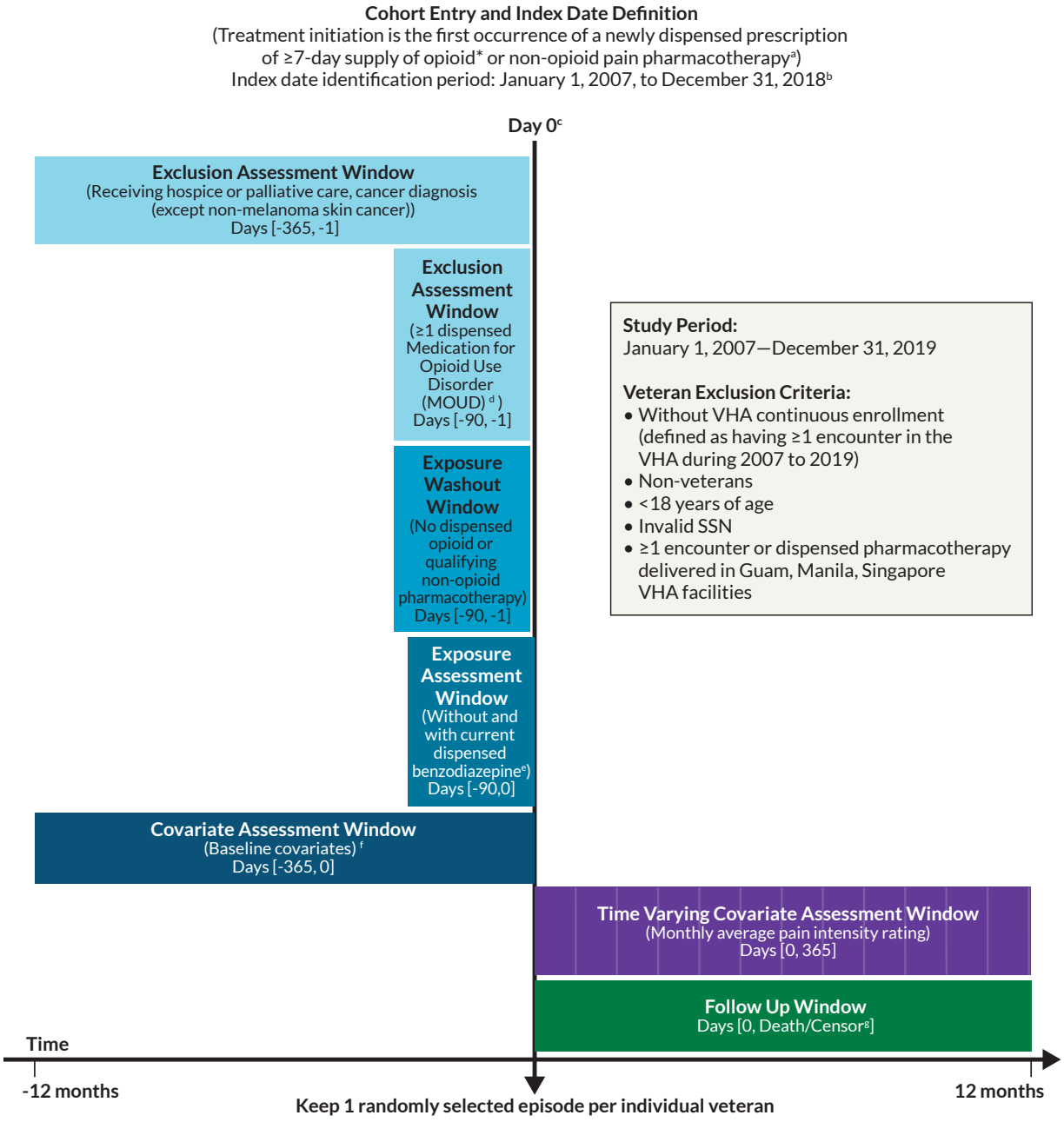

Notes:
*Opioid pharmacotherapy includes full agonist opioid pharmacotherapy, butorphanol, and tapentadol.
a. Baseline is defined at the first month in which all eligibility criteria are met. Episode: An interval of 30-day pharmacotherapy treatment created after first eligible dispensing of any opioid or non-opioid pain pharmacotherapy.
b. Index and follow-up: Every individual with an eligible dispensed prescription during the index date identification period is followed for 12 months through December 31, 2019 for all episodes. First eligible episodes starting after January 1, 2019 are not included.
c. Day 0 is individual dependent and is not anchored to a specific date.
d. MOUD formulations of buprenorphine, methadone, naltrexone, LAAM from prescription data.
e. Without current benzodiazepine pharmacotherapy: dispensed prescription of <5 tablets of benzodiazepine pharmacotherapy; with current benzodiazepine pharmacotherapy: dispensed prescription of ≥5 tablets.
f. The most recent values for age, sex, race, and ethnicity in individual electronic health records were used.
g. For intent to treat: eligible individuals are followed from the time of treatment initiation (baseline) until death (or death due to other causes, in analysis of suicide mortality), or the administrative end of follow-up (at the end of 12 months), whichever happens first.
Per Protocol: Eligible individuals are followed until all-cause and suicide mortality , non-adherence to treatment (>3 months without dispensed opioid pharmacotherapy), cancer diagnosis (except non-melanoma skin cancer), and/or receipt of hospice or palliative care during follow-up, whichever occurs first.

FIGURE 4-1 Study 1 design.

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Data from the national VHA data files were linked to the VA Corporate Data Warehouse, U.S. Veterans Eligibility Trends and Statistics, NDI, and Medicare Parts A, B, C, and D data from CMS. Primary sources for individual inclusion/exclusion and covariates were VA and VHA data. CMS data were used to supplement individual data used for inclusion/exclusion and other covariates. Data files were linked based on a combination of a veteran's unique individual integrated control number, Social Security number (SSN), and date of birth. The National Academies Institutional Review Board approved the study.

SPECIFICATIONS FOR THE EMULATED TARGET TRIAL 1

Drawing from this study population of all veterans receiving care in VHA facilities, the committee conducted two emulated trials or studies: Study 1a reflected veterans who were without current benzodiazepine pharmacotherapy and study 1b reflected veterans with current benzodiazepine pharmacotherapy. Each study compared mortality outcomes of those who were newly dispensed opioid pharmacotherapy with those newly dispensed non-opioid pain pharmacotherapy. Figure 4-2 illustrates the flowchart detailing the selection process of including eligible veterans in study 1. The following section outlines each of the target trial components for studies 1a and 1b.

Study 1 Eligibility Criteria

For each calendar month from January 1, 2007, to December 31, 2019, the committee identified eligible individuals who met the following criteria: (1) be a U.S. veteran; (2) be 18 years or older; (3) have a valid SSN; and (4) have at least 1 year of continuous enrollment in the VHA between 2006–2019, defined as at least one encounter in the VHA in the 12-month pre-index period. Eligible individuals also included veterans with at least one encounter in the VHA in the 12 months before index date within the eligible study period but only had a pharmacy claim through Medicare Part D (no VHA pharmacy claim). In addition, those who were eligible did not have an encounter or dispensed pharmacotherapy in Guam, Manila, or Singapore VHA facilities. These veterans were excluded given that mortality data collected in these regions are not reflected in the NDI data.

To be eligible for study 1a and study 1b, VHA veterans must have had no dispensed opioid pharmacotherapy or qualifying alternative non-opioid pain pharmacotherapy in the 90-day pre-index period (the exposure washout period). The committee established this washout period to exclude individuals with current dispensed opioid prescriptions in the VHA and relatively recent opioid or qualifying non-opioid pain prescription (VHA, 2006):

1. Maximum duration of any opioid prescription for non-hospice/non-palliative care is 90 days.
2. The maximum duration of any prescription fill in the VHA is 90 days, with exceptions for Schedule II drugs, such as oxycodone, which have a maximum duration of 30 days (except for individuals in hospice or palliative care).[7]

In addition, VHA veterans meeting the eligibility criteria must be dispensed ≥7-day supply of any qualifying opioid or non-opioid pain pharmacotherapy (Scully et al., 2018). Thus, the parameters used to determine this exposure washout period captured individuals newly dispensed opioid or non-opioid pain pharmacotherapy. Requiring a washout period facilitated the committee's ability to examine the effects of opioid pharmacotherapy among individuals newly dispensed it and avoid the issues described above that result from comparing across individuals with different treatment histories.

Study 1 Eligibility Exclusion

Studies 1a and 1b had an exclusion assessment window of 365 days before the index date. VHA veterans who received hospice or palliative care or had a cancer diagnosis (except non-melanoma skin cancers) were excluded.

[7] Hydrocodone was changed from a Schedule III drug to a Schedule II drug on October 6, 2014; before this, there could be 90-day fills of hydrocodone, which were common in the VA and private sector.

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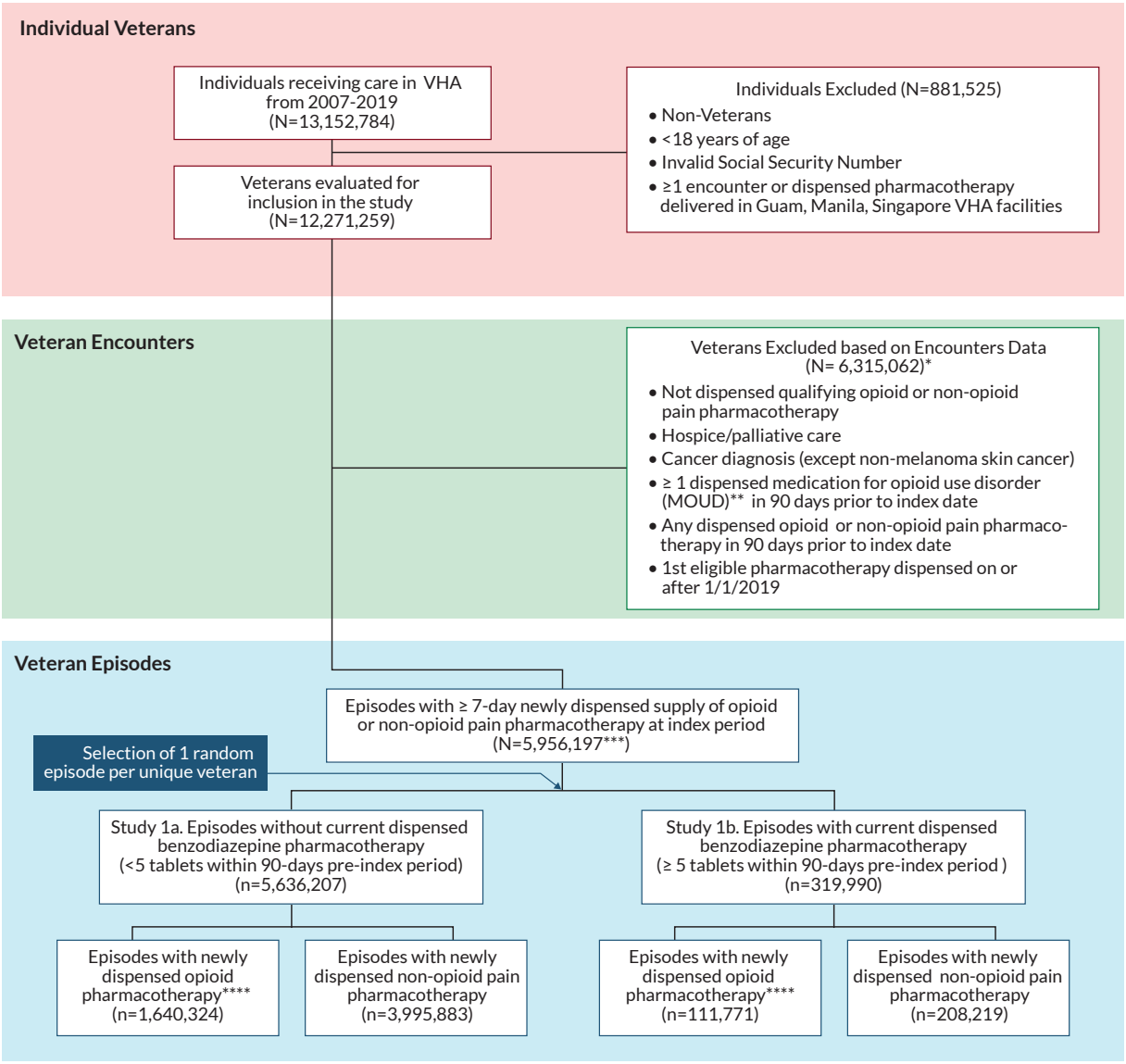

Note:
* Exclusions made prior to baseline (12 months, unless indicated otherwise) and not based on post-baseline information. See also Figure 4-1 exclusion assessment windows for timing information.
** Includes dispensed MOUD formulations of buprenorphine, methadone, LAAM, or naltrexone from prescription data.
***n=~18 million encounters.
**** Dispensed opioid or non-opioid pain pharmacotherapy at index. Includes (opioid only or both opioid and non-opioid pain pharmacotherapy). Opioid pharmacotherapy includes full agonist opioid pharmacotherapy, butorphanol, and tapentadol.

FIGURE 4-2 Selection of veterans in study 1 through each stage of the emulated target trial (2007–2019).
NOTE: No cell sizes of 10 or less are included in the reported result.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

International Classification of Disease (ICD) diagnosis codes were used to identify conditions (see Appendix I for list of codes). Individuals receiving palliative care and/or in hospice were excluded given that having a terminal illness (and thus being eligible for these services) is related to both death and more permissive opioid prescribing and thus is a confounder in the relationship between receiving opioid pharmacotherapy and death. In addition, individuals with cancer have an increased risk of mortality and often receive an opioid prescription to manage cancer-related pain. Decisions regarding opioid initiation, co-prescribing, and dosage increases may differ for cancer compared to non-cancer pain; policies and practices for opioid prescribing is (generally) more permissive for individuals with cancer (VA/DoD, 2022, 2017, 2010, 2003; Manchikanti et al., 2017; Dowell et al., 2016). Furthermore, the study exclusion criteria are in line with published studies examining opioid pharmacotherapy, which excluded individuals with cancer (Song et al., 2022; Coyle et al., 2018; Berna et al., 2015; Turner and Liang, 2015; Gomes et al., 2011; Dunn et al., 2010). As a result, having cancer may be a confounder between treatment regimen and mortality; therefore, individuals with cancer, other than non-melanoma skin cancer, are excluded.

The committee excluded VHA veterans receiving medications for opioid use disorder (MOUD) to reduce the likelihood of including those who were not truly opioid naïve. To ensure that individuals receiving MOUD treatment were excluded from the study, the committee determined that any individuals in the population who had received ≥1 dispensed MOUD formulation of levo-alpha acetyl methadol (LAAM), methadone, buprenorphine, or naltrexone in the 90-day pre-index period would be ineligible.

In studies 1a and 1b, veterans with all qualifying episodes[8] beginning on or after January 1, 2019, were excluded to ensure that each veteran included in the study had the potential for a complete 12-month follow-up period.

The causal question for this study focuses on the effect of newly dispensed opioid pharmacotherapy (i.e., initiating) versus newly dispensed non-opioid pain pharmacotherapy (i.e., initiating) among VHA veterans without (study 1a) and with (study 1b) current benzodiazepine pharmacotherapy. Studies 1a and 1b did not exclude individuals (a) receiving opioid pharmacotherapy who have an OUD or (b) with surgery or acute painful injury within the 90 days before the index date. The committee agreed that OUD diagnosis alone is not an absolute contraindication for opioid prescribing: the OUD diagnosis may not be recent, and individuals may not actively be receiving treatment during the time of the study. In addition, OUD was not considered a covariate by the committee because it is within the causal pathway of interest. Given these reasons, the committee did not exclude individuals with an OUD diagnosis. The committee aimed to capture all newly dispensed opioid pharmacotherapy exposure (except cancer-related and end-of-life pain, given the increased likelihood of mortality) (see Chapter 3 for more detail on the rationale).

Individuals may initially manage acute pain related to surgery, injuries, and/or other procedures using opioid or non-opioid pain pharmacotherapy and are sometimes prescribed longer-term pain pharmacotherapy (which may or may not include opioid pharmacotherapy) to manage chronic pain. Also, chronic pain often starts from an injury or experience that may be expected to result in short-term pain. By excluding these individuals, the sample would not be generalizable to individuals who experience this common pathway to chronic pain.

Study 1a and Study 1b Treatment Strategies

Drawing from this study population of eligible VHA veterans, studies 1a and 1b included veterans without and with currently dispensed benzodiazepine pharmacotherapy, respectively. Both studies focused on the initiation of clinically realistic treatment strategies:

- Study 1a: Of those without currently dispensed benzodiazepine pharmacotherapy,
  - those with a newly dispensed opioid pharmacotherapy (treatment group) versus
  - those with a newly dispensed non-opioid pain pharmacotherapy (comparator group)

and

- Study 1b: Of those with currently dispensed benzodiazepine pharmacotherapy,
  - those with a newly dispensed opioid pharmacotherapy (treatment group) versus
  - those with a newly dispensed non-opioid pain pharmacotherapy (comparator group)

[8] All veteran episodes (regardless of treatment assignment).

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The list of eligible opioid and non-opioid pain pharmacotherapies is in Table 4-2.

TABLE 4-2 Pharmacotherapies of Interest in Study 1

Drug Class	Study 1
Opioid Full Agonist	
Benzhydrocodone	Opioid pharmacotherapy (Treatment)
Codeine	Opioid pharmacotherapy (Treatment)
Dihydrocodeine	Opioid pharmacotherapy (Treatment)
Fentanyl	Opioid pharmacotherapy (Treatment)
Hydrocodone	Opioid pharmacotherapy (Treatment)
Hydromorphone	Opioid pharmacotherapy (Treatment)
LAAM[a] (non-liquid; for pain)	Opioid pharmacotherapy (Treatment)
LAAM (non-liquid; MOUD[b])	• Included in baseline exclusion criteria • Not censored during follow-up • Confounder during follow-up
Levomethadyl	Opioid pharmacotherapy (Treatment)
Levorphanol	Opioid pharmacotherapy (Treatment)
Meperidine (oral)	Opioid pharmacotherapy (Treatment)
Methadone (non-liquid/non-diskette) (for pain)	Opioid pharmacotherapy (Treatment)
Methadone (non-liquid/non-diskette) (MOUD)	• Included in baseline exclusion criteria • Not censored during follow-up • Confounder during follow-up
Morphine	Opioid pharmacotherapy (Treatment)
Oxycodone	Opioid pharmacotherapy (Treatment)
Oxymorphone	Opioid pharmacotherapy (Treatment)
Propoxyphene	Opioid pharmacotherapy (Treatment)
Sufentanil (sublingual)	Opioid pharmacotherapy (Treatment)
Tramadol	Opioid pharmacotherapy (Treatment)
Opioid Atypical	
Buprenorphine (MOUD)	• Included in baseline exclusion criteria • Not censored during follow-up • Confounder during follow-up
Buprenorphine (for pain)	• Included in baseline exclusion criteria • Not censored during follow-up • Confounder during follow-up

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-2 Continued

Drug Class	Study 1
Butorphanol	Opioid pharmacotherapy (Treatment)
Tapentadol	Opioid pharmacotherapy (Treatment)
Opioid Antagonist	
Naltrexone	• Included in baseline exclusion criteria • Not censored during follow-up • Confounder during follow-up
Benzodiazepine	
Alprazolam	Stratifying medication
Bromazepam	Stratifying medication
Chlordiazepoxide	Stratifying medication
Clobazam	Stratifying medication
Clonazepam	Stratifying medication
Clorazepate	Stratifying medication
Diazepam	Stratifying medication
Estazolam	Stratifying medication
Flurazepam	Stratifying medication
Halazepam	Stratifying medication
Lorazepam	Stratifying medication
Oxazepam	Stratifying medication
Prazepam	Stratifying medication
Quazepam	Stratifying medication
Remimazolam	Stratifying medication
Temazepam	Stratifying medication
Triazolam	Stratifying medication
Anti-Convulsant	
Carbamazepine	Confounder
Oxcarbazepine	Confounder
Topiramate	Confounder
Antidepressants	
Amitriptyline	Non-opioid pain pharmacotherapy (opioid comparator)
Amoxapine	Non-opioid pain pharmacotherapy (opioid comparator)
Bupropion (Tab)	Not included in study
Citalopram	Not included in study
Clomipramine	Non-opioid pain pharmacotherapy (opioid comparator)
Desipramine	Non-opioid pain pharmacotherapy (opioid comparator)
Desvenlafaxine	Confounder

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-2 Continued

Drug Class	Study 1
Doxepin	Non-opioid pain pharmacotherapy (opioid comparator)
Duloxetine	Non-opioid pain pharmacotherapy (opioid comparator)
Escitalopram	Not included in study
Esketamine	Not included in study
Fluoxetine	Not included in study
Fluvoxamine	Not included in study
Impramine	Non-opioid pain pharmacotherapy (opioid comparator)
Isocarboxazid	Not included in study
Levomilnacipran	Non-opioid pain pharmacotherapy (opioid comparator)
Milnacipran	Non-opioid pain pharmacotherapy (opioid comparator)
Mirtazapine	Confounder
Nefazodone	Not included in study
Nortriptyline	Non-opioid pain pharmacotherapy (opioid comparator)
Paroxetine	Not included in study
Phenelzine	Not included in study
Protriptyline	Non-opioid pain pharmacotherapy (opioid comparator)
Selegiline	Not included in study
Sertraline	Not included in study
Tranylcypromine	Not included in study
Trazodone	Not included in study
Trimipramine	Non-opioid pain pharmacotherapy (opioid comparator)
Venlafaxine	Confounder
Vilazodone	Not included in study
Viloxazine	Not included in study
Vortioxetine	Not included in study
Antihistamine	
Hydroxyzine	Confounder
Anxiolytic	
Buspirone	Confounder
Gabapentinoids	
Gabapentin	Non-opioid pain pharmacotherapy (opioid comparator)
Pregabalin	Non-opioid pain pharmacotherapy (opioid comparator)

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-2 Continued

Drug Class	Study 1
Insomnia	
Eszopiclone	Not included in study
Ramelteon	Not included in study
Suvorexant	Not included in study
Zaleplon	Not included in study
Zolpidem	Not included in study
Migraine	
Almotriptan	Confounder
Aspirin w/ caffeine	Confounder
Eletriptan	Confounder
Fioricet	Confounder
Fioridals	Confounder
Fioridan	Confounder
Frovatriptan	Confounder
Naratriptan	Confounder
Rizatriptan	Confounder
Sumatriptan	Confounder
Sumatriptan + Naproxen	Confounder
ZOLMitriptan	Confounder
Muscle Relaxers	
Baclofen	Non-opioid pain pharmacotherapy (opioid comparator)
Carisoprodol	Non-opioid pain pharmacotherapy (opioid comparator)
Chlorzoxazone	Non-opioid pain pharmacotherapy (opioid comparator)
Cyclobenzaprine	Non-opioid pain pharmacotherapy (opioid comparator)
Dantrolene	Non-opioid pain pharmacotherapy (opioid comparator)
Metaxalone	Non-opioid pain pharmacotherapy (opioid comparator)
Methocarbamol	Non-opioid pain pharmacotherapy (opioid comparator)
Orphenadrine	Non-opioid pain pharmacotherapy (opioid comparator)
Tizanidine	Non-opioid pain pharmacotherapy (opioid comparator)
Other Non-Opioid Analgesic	
Acetaminophen	Confounder
Non-Steroidal Anti-Inflammatory Drug	
Aspirin (>=400mg)	Non-opioid pain pharmacotherapy (opioid comparator)
Celecoxib	Non-opioid pain pharmacotherapy (opioid comparator)
Diclofenac (pill)	Non-opioid pain pharmacotherapy (opioid comparator)
Diflunisal	Non-opioid pain pharmacotherapy (opioid comparator)
Etodolac	Non-opioid pain pharmacotherapy (opioid comparator)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-2 Continued

Drug Class	Study 1
Fenoprofen	Non-opioid pain pharmacotherapy (opioid comparator)
Flurbiprofen	Non-opioid pain pharmacotherapy (opioid comparator)
Ibuprofen	Non-opioid pain pharmacotherapy (opioid comparator)
Indomethacin	Non-opioid pain pharmacotherapy (opioid comparator)
Ketoprofem	Non-opioid pain pharmacotherapy (opioid comparator)
Ketorolac	Non-opioid pain pharmacotherapy (opioid comparator)
Meclofenamate	Non-opioid pain pharmacotherapy (opioid comparator)
Meloxicam	Non-opioid pain pharmacotherapy (opioid comparator)
Nabumetone	Non-opioid pain pharmacotherapy (opioid comparator)
Naproxen	Non-opioid pain pharmacotherapy (opioid comparator)
Oxaprozin	Non-opioid pain pharmacotherapy (opioid comparator)
Phenylbutazone	Non-opioid pain pharmacotherapy (opioid comparator)
Piroxicam	Non-opioid pain pharmacotherapy (opioid comparator)
Salsalate	Non-opioid pain pharmacotherapy (opioid comparator)
Sulindac	Non-opioid pain pharmacotherapy (opioid comparator)
Tolmetin	Non-opioid pain pharmacotherapy (opioid comparator)
Serotonin-Norepinephrine Reuptake Inhibitor	
Desvenlafaxine	Confounder
Venlafaxine	Confounder
Tetracyclic Antidepressants	
Mirtazapine	Confounder

[a] LAAM = Levo-Alpha Acetyl Methadol.
[b] MOUD = medication for opioid use disorder.

Study 1a and Study 1b Treatment Assignment

In the hypothetical target trial, eligible individuals would be randomly assigned by clinical researchers to a treatment strategy with their consent and followed; individuals would be aware of their treatment assignment. In the emulated target trials (studies 1a and study 1b), based in retrospective observational data, assignments were based on the observed dispensed prescription drug events (claims) from Medicare Part D or dispensed pharmacotherapies from the VHA electronic health records (EHRs). Thus, the analyses considered prescription dispensing records to assign treatment strategy, unlike in the hypothetical target trial, for which the researchers would determine the assignment, which could be different from what medications[9] ultimately were dispensed. It is also important to distinguish the measurability of prescription dispensing data from the measurability of that which is ingested by the individual. A dispensed prescription does not necessarily mean that the medication was consumed, since these medications are commonly prescribed to be taken "as needed." For this study, a measure of individuals ingesting the prescription was not available in the dataset analyzed; the committee used prescription dispensing data as a proxy for medications ingested by the individual.

[9] The committee uses the term "pharmacotherapy" throughout the report instead of "medications," "prescriptions," or "treatment," especially when referencing the committee's analyses and results.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

After the first dispensed eligible pharmacotherapy, a 30-day pharmacotherapy episode interval was created for eligible VHA veterans. One episode per eligible veteran was selected at random for inclusion in the study.

Selection of Pharmacotherapies of Interest

Specifically, in studies 1a and 1b, the committee considered the initiation of two different clinically realistic treatment strategies: (1) opioid pharmacotherapy (i.e., the "exposure" of the target trial), and (2) non-opioid pain pharmacotherapy (i.e., the "comparator" of the target trial). Exposure to opioid pharmacotherapy was defined as having a dispensed opioid-containing pain pharmacotherapy with ≥7 days' supply. An eligible non-opioid pain pharmacotherapy (i.e., the "comparator") was defined as a dispensed qualifying non-opioid pain pharmacotherapy with ≥7 days' supply.

In addition, eligible VHA veterans for study 1 were stratified by the baseline status of current use of benzodiazepine pharmacotherapy. Those in study 1a (without current benzodiazepine pharmacotherapy) were defined as having <5 tablets of benzodiazepine pharmacotherapy within 90 days prior to the index date. Those in study 1b (with current benzodiazepine pharmacotherapy) were defined as having ≥5 tablets of benzodiazepine pharmacotherapy within 90 days prior to the index date. These thresholds were used to distinguish one-off use of benzodiazepine pharmacotherapy (e.g., magnetic resonance imaging (MRI), dental visit, flight anxiety).

Within studies 1a and study 1b, the treatment group are individuals newly dispensed opioid pharmacotherapy. Qualifying opioid pharmacotherapy included full agonist[10] opioid pharmacotherapy available for treatment during the study period (2007–2019). Additionally, two atypical opioid pharmacotherapies (tapentadol and butorphanol) were included due to their use in pain treatment and impact within the pain neurotransmitter route. The comparator group included individuals dispensed non-opioid pain pharmacotherapies with, but not limited to, primary indications for pain treatment (i.e., non-steroidal anti-inflammatory drugs (NSAIDs)). As many drugs have dual benefits and secondary indications, the drug list was expanded to include relevant pharmacotherapies with analgesic properties from several additional drug classes (tetracyclic antidepressant (TeCAs), serotonin-norepinephrine reuptake inhibitor (SNRIs), muscle relaxers, and gabapentinoids). Any individuals newly dispensed both opioid and non-opioid pain pharmacotherapy concurrently were included in the opioid treatment group.

Study 1a and Study 1b Start and End of Follow-Up

The start date, or the index date, is when the eligible VHA veteran was first dispensed the qualifying ≥7 days' supply of the opioid or non-opioid pain pharmacotherapy and when all baseline eligibility criteria were met. To facilitate computation, the index date was transformed into an index month, as the analyses were conducted using aggregated monthly data. Based on the study design that considered a 12-month pre-index period and a 12-month follow-up period, January 1, 2007, was the first eligible index date, and December 31, 2018, was the last eligible index date. The period of outcome measurement was 12 months from the index date, with a final follow-up date of December 31, 2019, which marked the end of the study period. The committee utilized all available follow-up data (through the end of 2020) with prespecified landmark analysis at 12 months.

For the per protocol analysis, given that interest is in observing the effect of initiating and continuing the treatment strategy over a specified follow-up period (sustained strategies), eligible individuals are followed from the time of treatment initiation (baseline) until death (or death due to other causes, in analysis of suicide mortality), cancer diagnosis (except non-melanoma skin cancer), receipt of hospice or palliative care, non-adherence to treatment (≥3 months without dispensed opioid pharmacotherapy) (or the administrative end of follow-up (at the end of 12 months from baseline), whichever happens first. For intent-to-treat (ITT) analysis, eligible individuals are followed from the time of treatment initiation (baseline) until death (or death due to other causes, in analysis of suicide mortality) or the administrative end of follow-up (at the end of 12 months), whichever happens first.

[10] There are two types of opioids: full agonist and partial opioid agonist. Full opioid agonists fully activate the mu receptors in the brain, enabling the opioid to have "full" effect, such as codeine, oxycodone, and fentanyl. Partial opioid agonists also activate mu receptors in the brain but to a lesser degree, such as butorphanol or tapentadol.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Study 1 Outcomes

The outcomes outlined in the statement of task are all-cause mortality and suicide mortality, which were identified through linked data from NDI. The committee determined all-cause mortality as the primary outcome and suicide mortality as the secondary outcome. Suicide mortality is identified by the ICD-10 death codes X60-X84 (intentional self-harm), U03 (intentional self-harm [suicide]), and Y87.0 (sequelae of intentional self-harm) (Hirsch et al., 2016; CDC, 2002).

Causal Contrast: Intent-to-Treat and Per Protocol Effects

Adhering to the statement of task and the causal question, this analysis focused on the effect of newly dispensed opioid versus non-opioid pain pharmacotherapy in study 1a (without current benzodiazepine pharmacotherapy) and study 1b (with current benzodiazepine pharmacotherapy), and these studies each employed two causal contrasts.

The primary causal contrast was the per protocol effect, which corresponds to the effect of adhering to the assigned treatment strategy during the follow-up. Individuals were censored if they stopped adhering to treatment protocol (i.e., ≥1 dispensed relevant pain pharmacotherapy). Each veteran contributed a maximum of 12 months to the analysis. An individual may have multiple episodes (with either opioid or non-opioid pharmacotherapy; a 90-day washout period would still be applied) during the study period; however, for the purposes of the analysis, one episode per individual was randomly selected. The committee considered selecting the first episode but was concerned of potential bias to earlier years of the study period. Preliminary analysis suggested that the distribution of outcomes and covariates were similar between the randomly selected episodes and the full sample of all veteran episodes.

The secondary causal contrast involved the ITT effect, which corresponds to the effect of being assigned to a treatment strategy (e.g., initiating opioid versus non-opioid pain pharmacotherapies at baseline), irrespective of subsequent cross-over or treatment discontinuation during follow-up.

For both per protocol and ITT analyses, the committee created 30-day pharmacotherapy episode intervals. In per protocol analysis, time-varying weights were created. In ITT, only baseline weights were created. For ITT analysis, the inverse probability was a function of only the baseline covariates; for per protocol analysis, it was a function of both baseline and time-varying covariates (Hernán and Robins, 2017; Robins et al., 2000).

The general assumption of this approach is if there are no unmeasured confounders, no measurement error, and no model misspecification, the per protocol and ITT effects are unbiased estimates of causal effects.

Study 1a and Study 1b Design

The study design was an active-comparator, new-user (Lund et al., 2015; Ray, 2003), retrospective cohort target trial emulation (Hernán and Robins, 2016). The emulated trial, using observational data, was conducted to estimate the effect of newly dispensed opioid pharmacotherapy versus non-opioid pain pharmacotherapy on mortality among VHA veterans without (study 1a) and with (study 1b) current use of benzodiazepine pharmacotherapy, for a follow-up period of 12 months.

Study 1a and Study 1b Covariates

To strengthen causal inferences, the committee controlled for many covariates to adjust for baseline and/or time-varying confounding and achieve balance between the treatment and comparator groups.

- Sociodemographics,
- Health conditions and behaviors,
- Supplemental health insurance to VHA coverage,
- Health care utilization,
- Specific pharmacotherapies,

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

- Facility,
- Facility-level characteristic, and
- Calendar month of eligible dispensed pharmacotherapy.

Additional covariates include month and the interaction of state and year as fixed effects. Baseline covariates included demographic characteristics (e.g., age, sex, race/ethnicity, marital status, disability status), supplemental insurance to VHA coverage (i.e., Medicare, TRICARE, or private insurance), housing security (e.g., history of homelessness status), physical and mental health conditions/disorders (e.g., acute painful injury, anxiety, chronic obstructive pulmonary disease, cardiovascular disease, substance use disorders, diabetes), military status (e.g., service era, military branch, combat service), body mass index, health care utilization in prior year (e.g., VHA outpatient visits, inpatient hospital admissions, nursing home stay), VHA facility-level characteristic (e.g., urbanicity), and specific pharmacotherapies that the committee considered as potential confounders (migraine pharmacotherapies, anxiolytics, and SNRIs; see Table 3-4 and Table 4-2 for the detailed list). The committee evaluated candidate variables readily available in the study clinical and administrative databases. See Appendix I for a list of all health conditions and corresponding ICD codes.

The studies did not require participants to have a chronic pain diagnosis in the primary analysis. Studies have shown that individuals identified with chronic pain did not have a pain diagnosis or pain was underreported in electronic medical records compared to pain reported in a patient-based survey (Frank et al., 2019; Goulet et al., 2016). In addition to this, chronic pain is an indication for the study model and can be widely assumed to be present given the study sample. Due to these reasons, the committee chose to not include it as a covariate in this study.

The committee controlled for several baseline confounders in this study. The committee, based on their expertise, excluded individuals at baseline with dispensed prescriptions for buprenorphine formulations for both OUD and pain treatment and naltrexone (an opioid antagonist) for OUD treatment. These pharmacotherapies were included as confounders if individuals were dispensed these pharmacotherapies after their index date during follow-up; individuals with these prescriptions may not be truly opioid naïve. The committee included specific antidepressants as confounders due to their off-label use to treat PTSD, tension type headaches (venlafaxine) and neuropathy (desvenlafaxine) (see Chapter 3 for rationale).

Lastly, based on a priori hypotheses that effects may vary by specific individual subgroups, the committee identified a subset of variables to be evaluated for effect modification (see the "Subgroup Analyses" section) (Suda et al., 2023; Gellad et al., 2018).

Time-Varying Covariates

The only time-varying covariate was pain intensity rating (pain scores)[11] (measured by the average of all documented pain scores within a month in the VHA EHR). The scores were updated monthly in the dataset and were incorporated in the inverse probability treatment weights (IPTWs), described later. When a new measurement was unavailable, the last observation was carried forward indefinitely until a new measurement was available or the individual was censored.

Accounting for Secular Trends and Variation by Facility

Facility and calendar time (12 months) were captured as fixed effects to capture facility-specific variation (e.g., clustering of individuals within a facility, geographic variations by facility) and reflect changes over time (e.g., variation in behaviors (health care seeking, prescribing)) and prevalence of conditions during a year. The committee also included an interaction term (i.e., product term) between state and year to capture variation over

[11] Pain scores refer to "pain intensity ratings" documented in the EHR Vital Signs package, which are derived from a routine standardized process that calls for screening for the presence and intensity of pain "right now" on a 0 (no pain) to 10 (worst pain imaginable) numeric rating scale when other vital signs are taken. They are therefore only routinely collected and documented when other vitals are taken (i.e., in primary care and other similar clinics and not in most specialty clinics, particularly not in mental health settings).

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time and by states, such as when state or facility policies related to opioid prescribing were implemented (e.g., when states began to participate in the Prescription Drug Monitoring Program) or secular trends in state-level policies and intensities during the opioid epidemic.

Statistical Analysis

The causal effects of studies 1a and study 1b were the per protocol effect of newly dispensed individuals who fully adhere to opioid versus non-opioid pain pharmacotherapy and the ITT effect of newly dispensed opioid versus non-opioid pain pharmacotherapy. For estimating both per protocol and ITT effects, an unadjusted and adjusted (IPTW) pooled logistic regression model was used to estimate the death rates (per 100,000 person-years) (as a measure of absolute risk) and hazard ratios (HR) for all-cause mortality and suicide mortality in the opioid treatment group, compared to the non-opioid treatment group serving as the reference. Wald confidence intervals (CIs) were used to estimate the 95 percent CIs. The survival curves for all-cause and suicide mortality over time by for those newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy (reference group) were estimated.

All analyses were conducted using SAS 9.4 and SAS Enterprise Guide. Study results do not report data if sample sizes were 10 or fewer individuals. This helps to ensure confidentiality of individuals in the study and be in line with CMS data policy and National Center for Health Statistics (NCHS) recommendations (NCHS, 2023; HHS, 2020). Furthermore, cells are marked as unreliable where sample sizes were 20 or fewer.

Accounting for Baseline Differences: Inverse Probability Treatment Weights

To account for the baseline difference between treatment and comparator groups in each target trial, analyses were weighted using IPTW for studies 1 and 3. IPTW is a method used to adjust for covariates and potential confounding in observational studies that uses a function of the propensity score (PS) of receiving treatment based on individual factors. By weighting each individual included in the analysis by the inverse of the probability of receiving the treatment or comparator treatment helps achieve balance between the treatment and comparator groups (Xu et al., 2010; Robins, 1986).

To calculate the IPTW,[12] the committee first performed a logistic regression to calculate the PS, or the likelihood of being in the treatment versus the comparator group. The PS was modeled by fitting a logistic regression of the medication received (treatment vs. control) as a function of the covariates described above. For per protocol analysis, IPTW was a function of both baseline and time-varying covariates; for ITT analysis, the IPTW was a function of only the baseline covariates (Robins et al., 2000). Second, the IPTW was calculated using the inverse of the PS, or 1/PS, for those in the newly dispensed opioid pharmacotherapy group (treatment) and 1/(1-PS) for those in the newly dispensed non-opioid pain pharmacotherapy group (comparator) in study 1a (without current benzodiazepine pharmacotherapy) and study 1b (with current benzodiazepine pharmacotherapy).

In each study, to limit the influence of extreme weights on the results, the committee winsorized weights to the middle 98 percent by applying the first percentile weight to all observations below the first percentile and the 99th percentile weight to all observations above the 99th percentile. In each study, the distribution of the PS by those in the treatment and comparator groups was depicted using histograms. In addition, the balance of baseline covariates between the two groups before and after IPTW was assessed using the absolute standardized mean difference (ASMD). An ASMD of ≤0.1 between the two groups after weighting suggests reduction of potential confounding, allowing for causal inference comparisons (Austin, 2009). Missing values were handled using the missing covariate indicator methods, which assigned a missing category in the model (e.g., Hispanic ethnicity, non-Hispanic ethnicity, missing ethnicity).

[12] More detail in calculating the IPTW for per protocol effect: to adjust for risk factors associated with treatment initiation (or adherence to treatment), time varying, non-stabilized IPTWs are estimated via a pooled logistic regression model for the monthly probability of treatment that includes the baseline and time-varying factors. The following weights were calculated: (1) a baseline treatment weight to adjust for measured confounding in the likelihood of initiating opioid versus non-opioid pharmacotherapy (the IPTW described); (2) an adherence weight (monthly); and (3) a censoring weight for loss to follow-up (monthly).

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Descriptive Analyses

The committee reports the distributions of baseline demographic and clinical characteristics for the overall analytic sample before and after application of the IPTW weights.

Subgroup Analysis

Given that examining the per protocol effect was the main analysis, subgroup analyses were based on that effect. Subgroup analyses were conducted by age (with two categorical comparisons: 18–64 versus ≥65 and 18–34, 35–54, 55–74, ≥75), race (White, Black, Native American/Alaskan Native, Asian, Hawaiian and Pacific Islander, more than one race, and missing), ethnicity (Hispanic and non-Hispanic), sex (male and female), time period (2007–2012 versus 2014–2019), and by payment source of dispensed medications (only Medicare Part D prescription claims, only VHA prescription claims, or both during the episode). The committee selected these subgroups to examine differences given older age groups, specific racial and ethnic groups, and males have been shown to be at increased risk for mortality (Bohnert and Ilgen, 2019; Bossarte et al., 2012). Age categories used in the national annual reports on veteran suicide prevention were also included in the subgroup analysis for consistency (VA, 2018).

The committee included time period as a subgroup to examine temporal changes in mortality risk. The committee selected before or after 2013, given the introduction of the VHA's OSI that year. The committee stratified by payment sources of dispensed opioid prescriptions during an episode: individuals were grouped as having prescriptions dispensed from only the VHA, only Medicare Part D, or both. Payment source of dispensed medication is a proxy for care, access, and coordination. Other research examining payment source suggest that multiple sources are associated with risky opioid prescribing, such as concurrent prescribing of opioid and benzodiazepine pharmacotherapy and prescribing with a high morphine milligram equivalents (MME)/day for opioid pharmacotherapy (Becker et al., 2017).

In addition, the committee repeated the main analysis for those with and without a recent surgery or outpatient procedure. This study included veterans with acute painful injury or inpatient/outpatient surgery/procedures because (1) the committee aims to focus on pain itself, (2) the treatment of acute pain can result in overdose or OUD, and (3) these individuals may initially manage acute pain related to surgery and/or other procedures using short-term opioid pharmacotherapy and are eventually prescribed opioid pharmacotherapy to manage chronic pain.

RESULTS

Among the 13,152,784 unique veterans who received care in the VHA 2007–2019, study 1 was split into two emulated target trials: Study 1a among veterans without and with a current dispensed benzodiazepine pharmacotherapy. Study 1a includes 5,636,207 unique veterans, further categorized as receiving either newly dispensed non-opioid pain pharmacotherapy (comparator group) or newly dispensed opioid pharmacotherapy (treatment group). The non-opioid pain pharmacotherapy group had 67,916 all-cause mortality and 1,094 suicide mortality deaths. The opioid pharmacotherapy group had 56,141 all-cause mortality and 566 suicide mortality deaths.

In Study 1b, there was a total of 319,990 unique veterans. Of these individuals, 208,219 were newly dispensed non-opioid pain pharmacotherapy and 111,771 were newly dispensed opioid pharmacotherapy. In the non-opioid pain pharmacotherapy group, there were 5,753 all-cause mortality and 197 suicide mortality deaths, and in the opioid pharmacotherapy group there were 5,369 all-cause mortality and 109 suicide mortality deaths.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Individuals Without a Current Dispensed Benzodiazepine (Study 1a)

Baseline Characteristics

In study 1a, 92.5 percent of participants were male, and the mean age was 60.2 years (SD[13]: 17.1). The racial distribution was 68.9 percent White, 17.9 percent Black, 0.9 percent Asian, 0.7 percent Native American, 0.8 percent Pacific Islander, and 0.8 percent multiracial or reporting more than race. About 10.1 percent were missing the race category. By ethnicity, 87.4 percent were of non-Hispanic ethnicity and 6.4 percent of Hispanic ethnicity. About 6.2 percent were missing the ethnicity category. Table 4-3 details the baseline characteristics of individuals newly dispensed opioid versus those newly dispensed non-opioid pain pharmacotherapy.

Before applying IPTW, baseline characteristics were generally similar between the treatment and comparator groups, except individuals newly dispensed opioid pharmacotherapy were more likely to be White, be in VA Priority Enrollment Group 5, to have rheumatic disease and to ever have Medicare Part D insurance coverage. After applying IPTW, covariates between both groups were well balanced, as indicated by all covariate ASMDs below 0.1. Approximately 20 percent of veterans in both groups had discontinued their initial treatment strategies by the 6-month follow-up (see supplement, Figures 4-7 and 4-12).

Mortality Outcomes

Table 4-4 presents the results for study 1a for all-cause and suicide mortality. In the per protocol analysis, the adjusted all-cause mortality rate was 6,473 per 100,000 person-years for those newly dispensed non-opioid pain pharmacotherapy versus 10,273 per 100,000 person-years for those newly dispensed opioid pharmacotherapy (adjusted HR: 1.61; 95% CI: 1.59–1.63). The ITT analysis resulted in an adjusted all-cause mortality rate of 4,952 versus 8,348 per 100,000 person-years for those newly dispensed opioid pharmacotherapy versus those newly dispensed non-opioid pain pharmacotherapy, respectively (adjusted HR: 1.69; 95% CI: 1.68–1.70).

For suicide mortality, the per protocol analysis resulted in an adjusted rate of 95 per 100,000 person-years for individuals newly dispensed non-opioid pain pharmacotherapy versus 112 per 100,000 person-years for individuals newly dispensed opioid pharmacotherapy (adjusted HR: 1.19; 95% CI: 1.07–1.32). In the ITT analysis, the suicide mortality rate was 65 versus 83 per 100,000 person-years for individuals newly dispensed non-opioid pain pharmacotherapy versus opioid pharmacotherapy (adjusted HR: 1.28; 95% CI: 1.20–1.37).

Survival curves demonstrate lower survival over time in those newly dispensed opioid pharmacotherapy, compared to those newly dispensed non-opioid pain pharmacotherapy among individuals without current benzodiazepine pharmacotherapy (see Figure 4-3).

Individuals with a Current Benzodiazepine Prescription (Study 1b)

Baseline Characteristics

For the cohort in study 1b, individuals were predominantly male (91.2 percent), and the mean age was 63.5 years (SD: 15.3). Racial distribution of veterans in study 1b was 78.9 percent White, 8.2 percent Black, 0.4 percent Asian, 0.6 percent Native American, 0.7 percent Pacific Islander, and 0.7 percent multiracial or reporting more than race. About 10.4 percent were missing the race category. By ethnicity, 87.1 percent of veterans were of non-Hispanic ethnicity and 6.6 percent Hispanic ethnicity. About 6.3 percent were missing the ethnicity category. Table 4-5 summarizes the baseline characteristics of individuals newly dispensed opioid pharmacotherapy versus individuals newly dispensed non-opioid pain pharmacotherapy among individuals with a current dispensed benzodiazepine pharmacotherapy, both before and after applying IPTW. The majority belonged to VHA enrollment priority group 1. Before IPTW weighting, baseline characteristics were generally similar between groups, with some exceptions (e.g., percent NSAID, see also Figure 4-6). After applying IPTW, covariate ASMDs were well

[13] SD: standard deviation

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4–3 Study 1a. Among Veterans Without a Current Dispensed Benzodiazepine Pharmacotherapy, Baseline Characteristics of Individuals Before and After Inverse Probability Treatment Weights (IPTW) (2007–2019; *N* = 5,636,207)

	Before Weighting			After IPTW		
Covariate	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD[1]**	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD**
Sex						
Male	93.75	91.89	0.07	92.31	92.43	0.00
Female	6.25	8.11	0.07	7.69	7.57	0.00
Missing	0.00	0.00	0.00	.	0.00	.
Age						
18–34	8.92	12.07	0.10	10.56	11.01	0.02
35–54	20.57	23.70	0.08	22.88	22.78	0.00
55–74	46.64	45.80	0.02	46.29	46.07	0.01
75+	23.87	18.44	0.13	20.27	20.15	0.00
Race						
White	71.85	67.65	0.09	68.36	68.83	0.01
Black	14.65	19.31	0.12	18.71	18.04	0.02
Asian	0.58	1.01	0.05	0.84	0.88	0.00
Native American	0.70	0.74	0.00	0.72	0.73	0.00
Pacific Islander	0.68	0.86	0.02	0.81	0.81	0.00
Multiracial	0.74	0.84	0.01	0.82	0.81	0.00
Missing	10.80	9.59	0.04	9.74	9.91	0.01
Ethnicity						
Non-Hispanic	87.94	87.34	0.02	87.51	87.51	0.00
Hispanic	5.20	6.90	0.07	6.54	6.43	0.01
Missing	6.87	5.76	0.05	5.95	6.06	0.01
Marital Status						
Married	51.06	50.44	0.01	50.40	50.54	0.00
Not Married	43.81	44.39	0.01	44.31	44.26	0.00
Missing	5.13	5.18	0.00	5.29	5.20	0.00
Disability Status *(Based on VA Enrollment Priority Group)*						
Enrollment Group 1	19.09	26.50	0.18	25.49	24.49	0.02
Enrollment Group 2	7.58	8.14	0.02	7.88	7.96	0.00
Enrollment Group 3	12.31	12.28	0.00	12.09	12.27	0.01
Enrollment Group 4	1.50	1.32	0.02	1.47	1.40	0.01
Enrollment Group 5	33.27	28.52	0.10	29.94	30.01	0.00

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4–3 Continued

	Before Weighting			After IPTW		
Covariate	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD[1]**	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD**
Enrollment Group 6	4.74	5.30	0.03	4.80	5.05	0.01
Enrollment Group 7	3.65	3.06	0.03	3.14	3.21	0.00
Enrollment Group 8	17.59	14.55	0.08	14.89	15.30	0.01
Missing	0.28	0.33	0.01	0.31	0.31	0.00
Housing Security						
History of homelessness (yes/no)	9.11	10.31	0.04	10.88	10.10	0.03
Health Behavior						
Tobacco Use Ever (yes/no)	44.70	41.98	0.06	43.68	42.99	0.01
Health Conditions						
Physical Health Conditions						
Acute Pain Injury	9.89	8.73	0.04	9.65	9.23	0.01
AIDS/HIV	0.42	0.39	0.01	0.43	0.40	0.00
Blood Loss Anemia	1.18	0.75	0.04	0.94	0.91	0.00
Cancer (non-melanoma skin)	0.34	0.22	0.02	0.26	0.26	0.00
Cardiovascular Disease	18.00	13.46	0.13	15.21	14.95	0.01
Cerebrovascular Disease	4.60	3.33	0.07	3.84	3.76	0.00
Chronic Lung Disease	13.58	11.29	0.07	12.50	12.11	0.01
Cirrhosis	1.03	0.60	0.05	0.79	0.79	0.00
COPD[2]	2.71	3.16	0.03	3.22	3.05	0.01
Deficiency Anemia	5.74	3.73	0.10	4.53	4.44	0.01
Dementia	2.64	2.52	0.01	2.72	2.60	0.01
Diabetes	20.37	21.23	0.02	21.47	21.09	0.01
ESRD[3]	0.91	0.48	0.05	0.64	0.62	0.00
Heart Disease	17.74	13.19	0.13	14.91	14.67	0.01
Hepatitis	1.45	1.30	0.01	1.49	1.39	0.01
Hemiplegia or Paraplegia	0.63	0.53	0.01	0.60	0.57	0.00

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4–3 Continued

	Before Weighting			After IPTW		
Covariate	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD[1]**	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD**
Liver Disease	2.17	1.77	0.03	1.97	1.96	0.00
Migraine	1.69	2.37	0.05	2.32	2.18	0.01
Peptic Ulcer Disease						
Peripheral Vascular Disease	4.20	3.25	0.05	3.68	3.58	0.01
Pulmonary Circulation Disorders	0.23	0.25	0.01	0.28	0.25	0.01
Rheumatic Disease	39.47	31.67	0.16	36.00	34.55	0.03
Syncope	0.51	0.49	0.00	0.54	0.50	0.01
Sleep Disorders						
Apnea	4.10	5.84	0.08	5.63	5.37	0.01
Insomnia	0.89	0.85	0.01	0.91	0.87	0.00
Mental Health						
ADHD[4]	0.16	0.15	0.00	0.15	0.15	0.00
Alcohol Use Disorder	2.64	3.56	0.05	3.56	3.32	0.01
Anxiety	3.35	3.56	0.01	3.70	3.54	0.01
Bipolar Disorder	1.03	1.37	0.03	1.37	1.28	0.01
Depression	7.59	7.68	0.00	8.26	7.77	0.02
Drug Use Disorder	1.21	1.88	0.06	1.96	1.70	0.02
Opioid Use Disorder	0.40	0.56	0.02	0.60	0.52	0.01
Posttraumatic Stress Disorder	6.44	7.55	0.04	7.73	7.30	0.02
Schizophrenia and Psychosis	0.77	1.18	0.04	1.15	1.07	0.01
Suicidal Ideation	0.18	0.33	0.03	0.34	0.29	0.01
TBI[5]	1.30	1.58	0.02	1.58	1.51	0.01
Overdose-Related Diagnoses						

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4–3 Continued

	Before Weighting			After IPTW		
Covariate	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD[1]**	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD**
Opioid Overdose Diagnosis (in last 12 months)	0.01	0.01	0.00	0.01	0.01	0.00
Current Pain Intensity Rating (in past month)						
Pain 0	32.44	38.77	0.13	35.12	36.45	0.03
Pain 1	4.15	3.95	0.01	3.96	3.99	0.00
Pain 2	4.97	4.76	0.01	4.81	4.81	0.00
Pain 3	6.64	6.41	0.01	6.62	6.50	0.01
Pain 4	6.30	5.90	0.02	6.23	6.05	0.01
Pain 5	6.86	6.35	0.02	6.83	6.57	0.01
Pain 6	5.64	5.10	0.02	5.58	5.34	0.01
Pain 7	5.51	4.81	0.03	5.36	5.12	0.01
Pain 8	5.25	4.21	0.05	4.90	4.64	0.01
Pain 9	2.15	1.55	0.04	1.91	1.79	0.01
Pain 10	1.95	1.36	0.05	1.70	1.60	0.01
Missing	18.13	16.83	0.03	16.98	17.14	0.00
Body Mass Index						
Underweight	1.14	0.79	0.04	0.91	0.91	0.00
Normal	19.35	17.67	0.04	18.06	18.17	0.00
Overweight	31.95	33.51	0.03	32.72	32.97	0.01
Obese	35.87	39.70	0.08	39.12	38.64	0.01
Missing	11.69	8.33	0.11	9.19	9.31	0.00
Health Care Coverage						
Supplemental Health Insurance to VHA Coverage	42.15	49.23	0.14	47.04	47.01	0.00
Medicare (ever/never)	19.06	9.74	0.27	12.71	12.60	0.00
Health Care Utilization in Past Year						
Number of VHA Outpatient Visits						
Outpatient Visits (0–4)	19.96	18.38	0.04	18.40	18.71	0.01

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4–3 Continued

	Before Weighting			After IPTW		
Covariate	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD[1]**	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD**
Outpatient Visits (4–11)	21.94	24.15	0.05	22.69	23.28	0.01
Outpatient Visits (12–21)	18.93	20.17	0.03	19.40	19.71	0.01
Outpatient Visits (22–42)	19.84	19.50	0.01	19.72	19.67	0.00
Outpatient Visits (43–67)	9.52	8.79	0.03	9.40	9.13	0.01
Outpatient Visits (68+)	9.81	9.01	0.03	10.39	9.50	0.03
Inpatient Hospital Admission	0.23	0.12	0.03	0.16	0.15	0.00
Inpatient Procedure/ Surgery	0.20	0.11	0.02	0.15	0.14	0.00
Inpatient Surgery						
Outpatient Procedure	0.68	0.48	0.03	0.57	0.55	0.00
Nursing Home Visit (Yes/No)	0.66	0.39	0.04	0.55	0.50	0.01
Military Status						
Service Era						
Gulf War	22.21	31.83	0.22	28.35	28.79	0.01
Korean War	9.99	7.47	0.09	8.27	8.23	0.00
Peacetime, only	17.48	15.83	0.04	16.62	16.37	0.01
Vietnam	36.30	33.95	0.05	34.79	34.71	0.00
WWII, only	8.40	5.56	0.11	6.53	6.47	0.00
Multiple Eras	3.58	3.76	0.01	3.75	3.71	0.00
Missing	2.05	1.60	0.03	1.70	1.73	0.00
Combat Service (yes/no)						
Combat Service	13.64	14.45	0.02	14.29	14.23	0.00
Missing	12.10	14.37	0.07	13.20	13.59	0.01
Military Sexual Trauma (yes/no)						
Military Sexual Trauma	3.61	4.43	0.04	4.37	4.21	0.01
Missing	2.52	2.08	0.03	2.16	2.19	0.00

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4–3 Continued

	Before Weighting			After IPTW		
Covariate	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD[1]**	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD**
Military Branch						
Air Force	11.37	12.00	0.02	11.74	11.80	0.00
Army	45.20	47.74	0.05	47.59	47.12	0.01
Marine	8.03	8.91	0.03	8.45	8.61	0.01
Navy	16.40	16.01	0.01	15.96	16.09	0.00
Missing	19.01	15.34	0.10	16.26	16.38	0.00
Prescription Information *(Yes/No)*						
Anticonvulsant	1.79	2.22	0.03	2.40	2.13	0.02
Antihistamine	4.42	4.98	0.03	5.24	4.87	0.02
Anxiolytic	1.64	2.04	0.03	2.09	1.95	0.01
Buprenorphine (for pain)	0.17	0.19	0.01	0.21	0.19	0.01
Migraine	3.13	4.21	0.06	4.52	3.95	0.03
Acetaminophen	66.67	21.20	1.03	34.87	35.00	0.00
SNRI[6]	2.74	2.81	0.00	3.00	2.83	0.01
TeCA[7]	3.77	3.54	0.01	3.92	3.68	0.01
Facility Urbanicity						
Non-Core	38.54	43.83	0.11	41.59	42.15	0.01
Micropolitan	7.15	7.48	0.01	7.27	7.32	0.00
Small Metro	24.16	27.15	0.07	26.53	26.34	0.00
Medium Metro	5.78	6.16	0.02	5.87	6.00	0.01
Large Fringe Metro	4.32	4.36	0.00	4.63	4.37	0.01
Large Central Metro	0.23	0.25	0.01	0.24	0.24	0.00
Missing	19.81	10.77	0.25	13.86	13.58	0.01

[1] ASMD: Absolute Standardized Mean Difference
[2] COPD: chronic obstructive pulmonary disease.
[3] ESRD: end-stage renal disease.
[4] ADHD: attention-deficit/hyperactivity disorder.
[5] TBI: traumatic brain injury.
[6] SNRI: serotonin-norepinephrine reuptake inhibitor
[7] TeCA: tetracyclic antidepressant
NOTE: No cell sizes of 10 or less are included in the reported results.

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TABLE 4-4 Study 1a. Among Veterans Without a Current Dispensed Benzodiazepine Pharmacotherapy, Unweighted and Adjusted All-Cause and Suicide Mortality Rates and Hazard Ratios in Veterans Newly Dispensed Opioid Pharmacotherapy Compared to Veterans Newly Dispensed Non-Opioid Pain Pharmacotherapy (2007–2019; N = 5,636,207)

	Unweighted					Adjusted*				
	Newly Dispensed Non-Opioid Pain Pharmacotherapy (n = 3,995,883)	**Newly Dispensed Opioid Pharmacotherapy (n = 1,640,324)**				**Newly Dispensed Non-Opioid Pain Pharmacotherapy (n = 3,995,883)**	**Newly Dispensed Opioid Pharmacotherapy (n = 1,640,324)**			
Outcome	*Rate per 100,000 person-years*	*Rate per 100,000 person-years*	**Hazard Ratio**	**95% CI Lower**	**95% CI Upper**	*Rate per 100,000 person-years*	*Rate per 100,000 person-years*	**Hazard Ratio**	**95% CI Lower**	**95% CI Upper**
All-cause mortality										
Per Protocol (Primary Analysis)	6,215	11,603	1.91	1.89	1.93	6,473	10,273	1.61	1.59	1.63
Intent to Treat (Secondary Analysis)	4,465	9,608	2.15	2.14	2.17	4,952	8,348	1.69	1.68	1.70
Suicide Mortality										
Per Protocol (Primary Analysis)	100	117	1.19	1.08	1.32	95	112	1.19	1.07	1.32
Intent to Treat (Secondary Analysis)	64	87	1.35	1.27	1.44	65	83	1.28	1.20	1.37

NOTES: No cell sizes of 10 or less are included in the reported results.
Adjusted: estimates based on application of inverse probablility treatment weights (IPTW).
A unique veteran is able to have multiple episodes. In study 1, for veterans with multiple episodes, only one episode was randomly selected.
CI = confidence interval.

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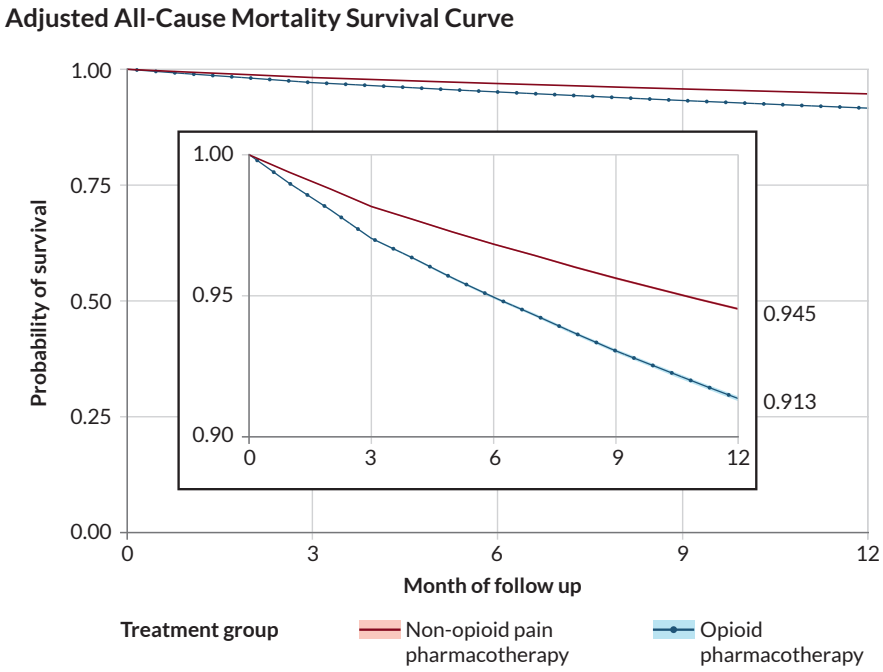
Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations



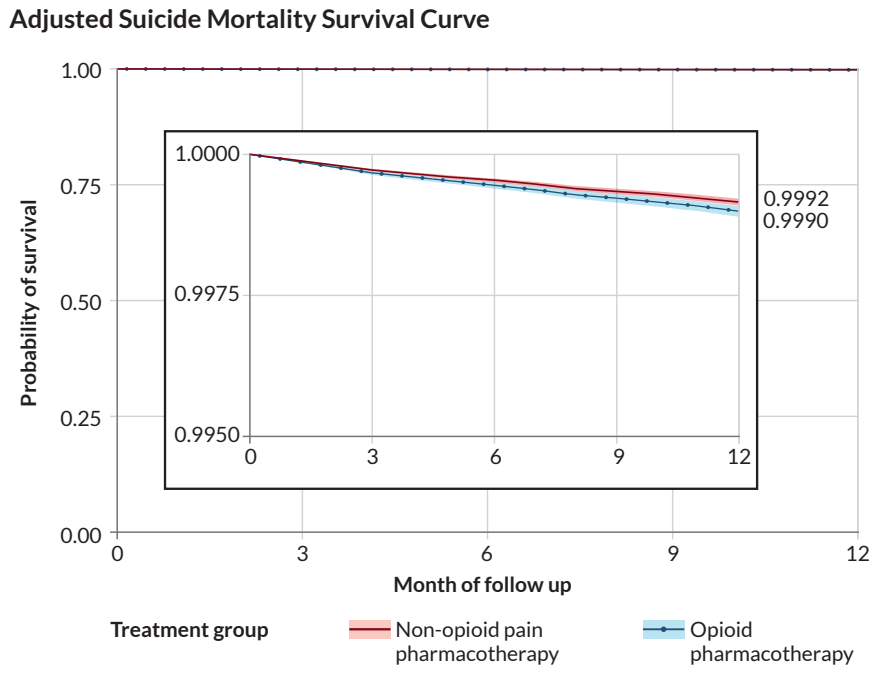


FIGURE 4-3 Study 1a. Among veterans without a current dispensed benzodiazepine pharmacotherapy, adjusted survival curves for all-cause mortality (top panel) and suicide mortality (bottom panel) in those newly dispensed opioid pharmacotherapy compared to veterans newly dispensed non-opioid pain pharmacotherapy (2007–2019; N = 5,636,207).
NOTES: No cells are reported representing 10 or fewer veterans. The y-axis range is compressed on the inset figure.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-5 Study 1b. Among Veterans with a Current Dispensed Benzodiazepine Pharmacotherapy, Baseline Characteristics of Individuals Before and After Inverse Probability Treatment Weights (IPTW) (2007–2019; *N* = 319,990)

	Before Weighting			After IPTW		
Covariate	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD**	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD**
Sex						
Male	91.95	90.56	0.05	90.91	90.97	0.00
Female	8.05	9.44	0.05	9.09	9.03	0.00
Age						
18–34	5.20	6.57	0.06	5.92	6.37	0.02
35–54	16.74	19.36	0.07	18.61	18.32	0.01
55–74	51.35	52.98	0.03	52.42	52.47	0.00
75+	26.71	21.10	0.13	23.05	22.85	0.01
Race						
White	79.55	78.80	0.02	78.95	78.94	0.00
Black	7.13	9.00	0.07	8.57	8.63	0.00
Asian	0.30	0.44	0.02	0.38	0.39	0.00
Native American	0.63	0.61	0.00	0.62	0.61	0.00
Pacific Islander	0.71	0.73	0.00	0.74	0.71	0.00
Multiracial	0.69	0.77	0.01	0.77	0.74	0.00
Missing	10.99	9.66	0.04	9.97	9.98	0.00
Ethnicity						
Non-Hispanic	87.65	87.00	0.02	86.75	87.26	0.02
Hispanic	5.55	7.34	0.07	7.28	6.77	0.02
Missing	6.79	5.65	0.05	5.97	5.97	0.00
Marital Status						
Married	52.51	51.30	0.02	51.44	51.50	0.00
Not Married	41.77	42.68	0.02	42.43	42.59	0.00
Missing	5.72	6.02	0.01	6.13	5.92	0.01
Disability Status *(Based on VA[1] Enrollment Priority Group)*						
Enrollment Group 1	32.67	42.22	0.20	39.38	39.03	0.01
Enrollment Group 2	6.28	5.94	0.01	6.07	6.39	0.01
Enrollment Group 3	8.70	7.81	0.03	8.05	8.04	0.00
Enrollment Group 4	2.30	2.32	0.00	2.38	2.43	0.00
Enrollment Group 5	29.34	24.94	0.10	26.54	26.33	0.01
Enrollment Group 6	2.41	2.39	0.00	2.29	2.34	0.00
Enrollment Group 7	2.76	2.19	0.04	2.31	2.33	0.00
Enrollment Group 8	15.33	12.02	0.10	12.80	12.93	0.00
Missing	0.20	0.18	0.00	0.19	0.19	0.00

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4–5 Continued

	Before Weighting			After IPTW		
Covariate	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD**	**Newly Dispensed Opioid Pharmacotherapy**	**Newly Dispensed Non-Opioid Pain Pharmacotherapy**	**ASMD**
Housing Security						
History of homelessness (yes/no)	8.83	10.24	0.05	10.20	9.85	0.01
Health Behavior						
Tobacco Use Ever (yes/no)	50.19	49.86	0.01	50.48	50.26	0.01
Health Conditions						
Physical Health Conditions						
Acute Pain Injury	12.66	12.34	0.01	13.17	12.52	0.02
AIDS/HIV	0.52	0.48	0.01	0.49	0.49	0.00
Blood Loss Anemia	1.63	1.16	0.04	1.40	1.35	0.00
Cancer (non-melanoma skin)	0.34	0.29	0.01	0.32	0.31	0.00
Cardiovascular Disease	25.18	20.34	0.12	22.28	21.92	0.01
Cerebrovascular Disease	6.46	5.14	0.06	5.64	5.58	0.00
Chronic Lung Disease	21.47	18.82	0.07	20.15	19.70	0.01
Cirrhosis	1.33	0.84	0.05	1.09	1.06	0.00
COPD[2]	4.40	4.72	0.02	4.66	4.56	0.00
Deficiency Anemia	7.43	5.40	0.08	6.28	6.17	0.01
Dementia	4.95	5.13	0.01	5.16	5.06	0.00
Diabetes	23.36	25.05	0.04	24.89	24.44	0.01
End-Stage Renal Disease	1.17	0.63	0.06	0.83	0.82	0.00
Heart Disease	24.86	20.03	0.12	21.96	21.62	0.01
Hepatitis	1.99	1.81	0.01	2.00	2.01	0.00
Hemiplegia or Paraplegia	0.88	0.93	0.01	0.92	0.91	0.00
Liver Disease	2.75	2.42	0.02	2.67	2.58	0.01
Migraine	3.22	3.86	0.04	3.77	3.64	0.01
Peptic Ulcer Disease	0.99	0.67	0.04	0.84	0.81	0.00
Peripheral Vascular Disease	5.06	4.13	0.04	4.52	4.43	0.00
Pulmonary Circulation Disorders	0.24	0.29	0.01	0.29	0.27	0.00
Rheumatic Disease	47.78	40.96	0.14	45.27	43.84	0.03
Syncope	0.79	0.84	0.01	0.90	0.84	0.01

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4–5 Continued

Covariate	Before Weighting			After IPTW		
	Newly Dispensed Opioid Pharmacotherapy	Newly Dispensed Non-Opioid Pain Pharmacotherapy	ASMD	Newly Dispensed Opioid Pharmacotherapy	Newly Dispensed Non-Opioid Pain Pharmacotherapy	ASMD
Sleep Disorders						
Apnea	5.33	7.24	0.08	6.70	6.66	0.00
Insomnia	4.01	3.81	0.01	3.96	3.85	0.01
Mental Health						
ADHD[3]	0.48	0.48	0.00	0.49	0.59	0.01
Alcohol Use Disorder	3.81	4.92	0.05	4.77	5.01	0.01
Anxiety	21.93	22.98	0.03	22.72	22.55	0.00
Bipolar Disorder	4.81	6.05	0.06	5.74	5.58	0.01
Depression	24.07	24.76	0.02	25.12	24.44	0.02
Drug Use Disorder	1.73	2.41	0.05	2.42	2.29	0.01
Opioid Use Disorder	0.74	0.88	0.02	0.93	0.95	0.00
Posttraumatic Stress Disorder	23.18	26.08	0.07	25.51	25.39	0.00
Schizophrenia and Psychosis	2.73	4.56	0.10	4.00	3.88	0.01
Suicidal Ideation	0.52	0.83	0.04	0.78	0.83	0.01
Traumatic Brain Injury	2.16	2.62	0.03	2.55	2.45	0.01
Overdose-Related Diagnoses						
Opioid Overdose Diagnosis (in last 12 months)	0.04	0.03	0.01	0.03	0.03	0.00
Current Pain Intensity Rating (in past month)						
Pain 0	30.87	38.33	0.16	34.35	35.50	0.02
Pain 1	3.83	4.04	0.01	4.05	3.93	0.01
Pain 2	4.64	4.58	0.00	4.70	4.58	0.01
Pain 3	6.63	6.28	0.01	6.60	6.38	0.01
Pain 4	6.22	5.51	0.03	5.91	6.09	0.01
Pain 5	7.01	6.06	0.04	6.61	6.41	0.01
Pain 6	5.79	4.84	0.04	5.43	5.32	0.01
Pain 7	5.77	4.68	0.05	5.32	5.11	0.01
Pain 8	5.39	4.18	0.06	4.91	4.67	0.01
Pain 9	2.18	1.58	0.04	1.89	1.82	0.01
Pain 10	1.80	1.30	0.04	1.57	1.51	0.01
Missing	19.87	18.62	0.03	18.64	18.68	0.00
Body Mass Index						
Underweight	1.37	0.97	0.04	1.12	1.09	0.00
Normal	20.99	19.16	0.05	19.65	20.04	0.01
Overweight	32.93	34.32	0.03	33.62	33.83	0.00
Obese	34.63	38.04	0.07	37.37	36.74	0.01
Missing	10.09	7.50	0.09	8.24	8.29	0.00

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4–5 Continued

Covariate	Before Weighting: Newly Dispensed Opioid Pharmacotherapy	Before Weighting: Newly Dispensed Non-Opioid Pain Pharmacotherapy	Before Weighting: ASMD	After IPTW: Newly Dispensed Opioid Pharmacotherapy	After IPTW: Newly Dispensed Non-Opioid Pain Pharmacotherapy	After IPTW: ASMD
Health Care Coverage						
Supplemental Health Insurance to VHA[4] Coverage	39.79	47.75	0.16	44.84	45.08	0.01
Medicare (ever/never)	23.30	13.38	0.26	16.80	16.58	0.01
Health Care Utilization in Past Year						
Number of VA Outpatient Visits						
VA Outpatient Visits (0–4)	8.50	5.47	0.12	6.52	6.44	0.00
VA Outpatient Visits (4–11)	14.94	13.38	0.05	13.42	13.60	0.01
VA Outpatient Visits (12–21)	18.01	18.91	0.02	18.01	18.24	0.01
VA Outpatient Visits (22–42)	24.85	26.78	0.04	25.86	26.53	0.02
VA Outpatient Visits (43–67)	15.01	15.81	0.02	15.70	15.64	0.00
VA Outpatient Visits (68+)	18.70	19.64	0.02	20.48	19.54	0.02
Inpatient Hospital Admission	0.21	0.15	0.01	0.17	0.16	0.00
Inpatient Procedure	0.19	0.15	0.01	0.18	0.17	0.00
Inpatient Procedure/ Inpatient Surgery						
Outpatient Procedure	0.88	0.72	0.02	0.83	0.77	0.01
Nursing Home Visit (Yes/No)	0.71	0.51	0.03	0.63	0.59	0.01
Military Status						
Service Era						
Gulf War	15.11	20.56	0.14	18.45	19.15	0.02
Korean War	11.55	8.91	0.09	9.84	9.74	0.00
Peacetime, only	16.93	16.05	0.02	16.49	16.22	0.01
Vietnam	41.36	42.56	0.02	42.17	41.85	0.01
WWII, only	9.60	6.94	0.10	7.94	7.84	0.00
Multiple Eras	3.13	3.33	0.01	3.26	3.36	0.01
Missing	2.31	1.65	0.05	1.85	1.84	0.00
Combat Service (yes/no)						
Combat Service	17.26	18.27	0.03	17.95	18.15	0.01
Missing	9.12	9.97	0.03	9.45	9.51	0.00
Military Sexual Trauma (yes/no)						
Military Sexual Trauma	6.25	7.47	0.05	7.28	7.14	0.01
Missing	2.17	1.99	0.01	2.06	2.02	0.00
Military Branch						
Air Force	11.11	11.56	0.01	11.44	11.26	0.01

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4–5 Continued

Covariate	Before Weighting			After IPTW		
	Newly Dispensed Opioid Pharmacotherapy	Newly Dispensed Non-Opioid Pain Pharmacotherapy	ASMD	Newly Dispensed Opioid Pharmacotherapy	Newly Dispensed Non-Opioid Pain Pharmacotherapy	ASMD
Army	47.14	49.84	0.05	49.10	48.91	0.00
Marine	6.70	7.22	0.02	7.02	7.32	0.01
Navy	15.88	15.58	0.01	15.60	15.64	0.00
Missing	19.18	15.80	0.09	16.84	16.88	0.00
Prescription Information ***(Yes/No)***						
Anticonvulsant	4.02	4.86	0.04	4.83	4.56	0.01
Antihistamine	7.37	8.51	0.04	8.37	8.50	0.00
Anxiolytic	4.38	5.75	0.06	5.38	5.24	0.01
Buprenorphine (for pain)	0.30	0.26	0.01	0.29	0.27	0.00
Migraine	5.67	6.68	0.04	6.79	6.36	0.02
Acetaminophen	69.42	28.63	0.89	43.28	42.81	0.01
SNRI[5]	7.91	8.84	0.03	8.62	8.46	0.01
TeCA[6]	9.87	10.05	0.01	10.27	9.98	0.01
Facility Urbanicity						
Non-Core	32.78	37.61	0.10	35.43	36.25	0.02
Micropolitan	7.27	7.57	0.01	7.43	7.37	0.00
Small Metro	23.04	26.19	0.07	25.15	24.93	0.01
Medium Metro	6.88	7.61	0.03	7.29	7.25	0.00
Large Fringe Metro	4.51	4.54	0.00	4.64	4.77	0.01
Large Central Metro	0.34	0.40	0.01	0.36	0.37	0.00
Missing	25.17	16.08	0.23	19.70	19.07	0.02

[1] VA: Department of Veterans Affairs
[2] COPD: Chronic obstructive pulmonary disease.
[3] ADHD: Attention-deficit/hyperactivity disorder.
[4] VHA: Veterans Health Administration.
[5] SNRI: Serotonin-norepinephrine reuptake inhibitor.
[6] TeCA: Tetracyclic antidepressant.
NOTE: No cells are reported representing 10 or fewer veterans.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

below 0.1, indicating good balance between the groups (see supplement Figure 4-11). Supplement Figures 4-7 and 4-12 illustrate adherence to treatment strategies, which was generally similar across treatment groups. By the 6-month follow-up, approximately 30 percent of veterans in both groups had discontinued their initial treatment strategies.

Mortality Outcomes

Among individuals with a current dispensed benzodiazepine pharmacotherapy prescription, Table 4-6 presents the results from the per protocol and ITT analyses comparing mortality between individuals newly dispensed opioid pharmacotherapy versus individuals newly dispensed non-opioid pain pharmacotherapy.

Based on results of the per protocol analysis, the adjusted all-cause mortality rate was 7,441 deaths per 100,000 person-years in the newly dispensed non-opioid pain pharmacotherapy group and 11,877 deaths per 100,000 person-years in the newly dispensed opioid pharmacotherapy group, resulting in an adjusted HR for all-cause mortality of 1.59 (95% CI: 1.53–1.65). The ITT analysis resulted in adjusted all-cause mortality rate of 7,037 deaths per 100,000 person-years for individuals newly dispensed non-opioid pain pharmacotherapy versus 10,850 deaths per 100,000 person-years for individuals newly dispensed opioid pharmacotherapy (adjusted HR: 1.54; 95% CI: 1.50–1.58).

For suicide mortality, the per protocol analysis resulted in an adjusted mortality rate of 238 deaths per 100,000 person-years in the newly dispensed non-opioid pain pharmacotherapy compared to 246 deaths per 100,000 person-years for the newly dispensed opioid pharmacotherapy treatment group (adjusted HR: 1.03; 95% CI: 0.81–1.31). In the ITT analysis, the suicide mortality rate was 189 deaths versus 200 deaths per 100,000 person-years for individuals newly dispensed non-opioid pain pharmacotherapy versus individuals newly dispensed opioid pharmacotherapy (adjusted HR: 1.06; 95% CI: 0.90–1.26).

Survival curves demonstrate lower survival over time in those newly dispensed opioid pharmacotherapy, compared to those dispensed non-opioid pain pharmacotherapy among individuals with current benzodiazepine pharmacotherapy (see Figure 4-4).

Subgroup Analyses

Results from subgroup analyses of the per protocol effect from study 1a (individuals without a current dispensed benzodiazepine pharmacotherapy) were largely consistent with the overall adjusted HR, with a few notable exceptions. Tables 4-7 and 4-8 present the mortality rates and HRs for all-cause mortality and suicide mortality among individuals without a current benzodiazepine pharmacotherapy by various subgroups.

For study 1b (individuals with current dispensed benzodiazepine pharmacotherapy), subgroup per protocol estimates were similar in magnitude and direction to the overall results for both all-cause and suicide mortality, with a few exceptions. For instance, the adjusted HR for all-cause mortality was higher among veterans whose pain pharmacotherapy claims were dispensed from only Medicare Part D; the higher adjusted HR, which was observed in both studies 1a and 1b (with and without a current benzodiazepine pharmacotherapy). Tables 4-9 and 4-10 present the adjusted mortality rates and HRs for all-cause mortality and suicide mortality among individuals with a current dispensed benzodiazepine pharmacotherapy by various subgroups.

See supplementary Tables 4-11 and 4-12 and Figures 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 4-11, 4-12, 4-13, and 4-14 for further details.

DISCUSSION

Studies 1a and 1b examined the effect of newly dispensed opioid pharmacotherapy on all-cause mortality and suicide mortality in two groups of veterans receiving care at the VHA: individuals without a current benzodiazepine pharmacotherapy (study 1a) and individuals with a current benzodiazepine pharmacotherapy (study 1b). The study was conducted in response to two parts of the statement of task to examine (a) the effect of opioid prescribing, relative to alternative non-opioid treatments, and (d) the effect of initiating opioids among veterans

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TABLE 4-6 Study 1b. Among Veterans with Current Dispensed Benzodiazepine Pharmacotherapy, Unweighted and Adjusted All-Cause and Suicide Mortality Rates and Hazard Ratios in Veterans Newly Dispensed Opioid Pharmacotherapy Compared to Veterans Newly Dispensed Non-opioid Pain Pharmacotherapy (2007–2019; *N* = 319,990)

	Unweighted					**Adjusted***				
	Newly Dispensed Non-Opioid Pain Pharmacotherapy (*N* = 208,219)	**Newly Dispensed Opioid Pharmacotherapy (*N* = 111,771)**				**Newly Dispensed Non-Opioid Pain Pharmacotherapy (*N* = 208,219)**	**Newly Dispensed Opioid Pharmacotherapy (*N* = 111,771)**			
Outcome	*Death per 100,000 person-years*	*Death per 100,000 person-years*	**Hazard Ratio**	**95% CI Lower**	**95% CI Upper**	*Death per 100,000 person-years*	*Death per 100,000 person-years*	**Hazard Ratio**	**95% CI Lower**	**95% CI Upper**
All-cause Mortality										
Per Protocol (Primary Analysis)	7,249	12,792	1.77	1.71	1.84	7,441	11,877	1.59	1.53	1.65
Intent to Treat (Secondary Analysis)	6,567	11,974	1.82	1.78	1.87	7,037	10,850	1.54	1.50	1.58
Suicide Mortality										
Per Protocol (Primary Analysis)	248	260	1.05	0.83	1.33	238	246	1.03	0.81	1.31
Intent to Treat (Secondary Analysis)	188	202	1.07	0.91	1.27	189	200	1.06	0.90	1.26

NOTES: No cell sizes of 10 or less are included in the reported results.
Adjusted = estimates based on application of inverse probably treatment weights (IPTW), CI = confidence interval.
A unique veteran is able to have multiple episodes. In Study 1, for veterans with multiple episodes, only one episode was randomly selected.

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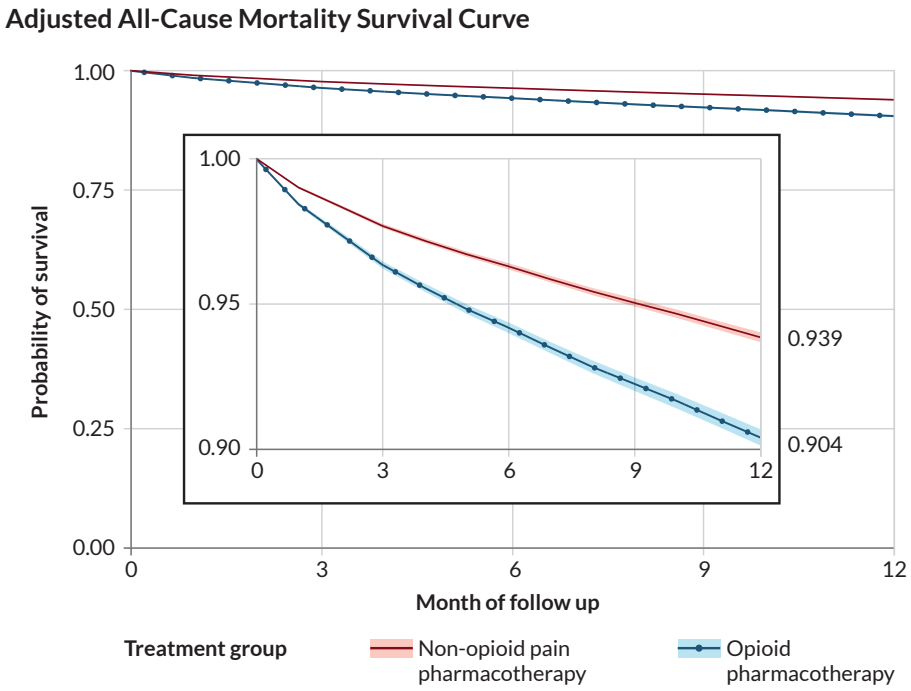

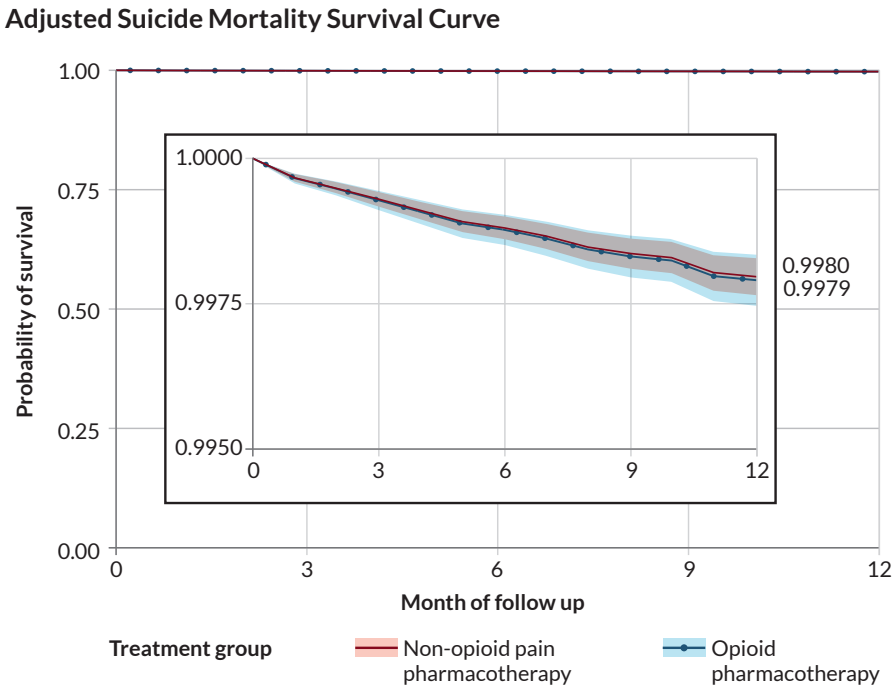

FIGURE 4-4 Study 1b. Among veterans with a current dispensed benzodiazepine pharmacotherapy, adjusted survival curves for all-cause mortality (top panel) and suicide mortality (bottom panel) in those newly dispensed opioid pharmacotherapy compared to veterans newly dispensed non-opioid pain pharmacotherapy (2007–2019; $N = 319{,}990$).
NOTE: No cells are reported representing 10 or fewer veterans. In the insert figure, the y-range is compressed.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-7 Study 1a. Subgroup Results—All-Cause Mortality: Among Veterans Without Current Dispensed Benzodiazepine Pharmacotherapy, Adjusted Mortality Rates and Hazard Ratios of All-Cause Mortality Between Individuals Newly Dispensed Opioid Pharmacotherapy Compared to Those Newly Dispensed Non-Opioid Pain Pharmacotherapy by Subgroups (2007–2019; N = 5,636,207)

All-Cause Mortality	Without Current Benzodiazepine Pharmacotherapy		
	Adjusted		
	All-Cause Mortality Death Rate		Hazard ratio (CI[1])
Sensitivity Analysis	Newly Dispensed Non-opioid Pain Pharmacotherapy	Newly Dispensed Opioid Pharmacotherapy	
OVERALL	6,473	10,273	1.61 (1.59–1.63)
Insurance Coverage			
CMS only	15,163	35,566	2.27 (2.23–2.31)
DUAL: both VHA / CMS	4,283	4,886	1.15 (1.10–1.20)
VHA only	5,084	5,989	1.20 (1.18–1.22)
Sex			
Gender—male	6,803	10,775	1.60 (1.58–1.62)
Gender—female	1,936	3,198	1.66 (1.52–1.81)
Age ≤65+			
18–64	2,377	3,078	1.31 (1.28–1.35)
65+	11,126	20,159	1.79 (1.77–1.81)
Age (Categorical)			
18–34	704	830	1.15 (0.99–1.33)
35–54	1,532	1,983	1.31 (1.24–1.38)
55–74	4,347	6,421	1.49 (1.46–1.53)
75+	17,719	32,655	1.80 (1.77–1.82)
Ethnicity			
Hispanic (no)	6,037	9,513	1.60 (1.58–1.62)
Hispanic (yes)	4,166	5,985	1.45 (1.35–1.55)
Hispanic (missing)	14,644	26,034	1.78 (1.73–1.83)
Race			
White	6,248	10,012	1.62 (1.60–1.65)
Black	4,256	5,986	1.42 (1.37–1.48)
Asian	2,882	11,126	3.93 (3.31–4.66)
Hawaiian	5,277	8,335	1.60 (1.37–1.87)
Native	4,902	5,607	1.15 (0.97–1.36)
Multi	4,341	5,886	1.38 (1.16–1.64)
Missing	12,326	20,694	1.69 (1.65–1.74)
Surgical Procedure			
Surgery/Procedure	8,755	13,151	1.49 (1.39–1.61)
No Surgery/Procedure	6,423	10,221	1.61 (1.59–1.63)
Study Year			
Study Year 2007–2012	7,735	11,459	1.51 (1.49–1.53)
Study Year 2014–2019	5,327	8,697	1.64 (1.61–1.68)

[1] CI: Confidence Interval.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-8 Study 1a. Subgroup Results—Suicide Mortality: Among Veterans Without Current Benzodiazepine Pharmacotherapy, Adjusted Mortality Rates and Hazard Ratios of Suicide Mortality Between Individuals Newly Dispensed Opioid Pharmacotherapy Compared to Those Newly Dispensed Non-Opioid Pain Pharmacotherapy by Subgroups (2007–2019; *N* = 5,636,207)

Suicide Mortality	**Without Current Benzodiazepine Pharmacotherapy**		
	Adjusted		
	Suicide Mortality Death Rate		
Sensitivity Analysis	**Newly Dispensed Non-opioid Pain Pharmacotherapy**	**Newly Dispensed Opioid Pharmacotherapy**	**Hazard ratio (CI)**
OVERALL	95	112	1.19 (1.07–1.32)
Insurance Coverage			
CMS only	68	118	1.68 (1.27–2.22)
DUAL: both VHA / CMS	35	49	1.44 (0.93–2.21)
VHA only	116	118	1.03 (0.91–1.17)
Sex			
Gender—male	99	115	1.17 (1.05–1.31)
Gender—female	44	55	1.28 (0.69–2.39)
Age ≤65+			
18–64	121	114	0.96 (0.84–1.11)
65+	70	108	1.52 (1.28–1.81)
Age (Categorical)			
18–34	214	168	0.78 (0.57–1.06)
35–54	139	124	0.91 (0.73–1.12)
55–74	72	101	1.42 (1.20–1.67)
75+	74	122	1.58 (1.25–1.99)
Ethnicity			
Hispanic (no)	91	111	1.23 (1.10–1.38)
Hispanic (yes)	74	63	0.86 (0.45–1.61)
Hispanic (missing)	173	217	1.26 (0.93–1.70)
Race			
White	101	122	1.22 (1.08–1.38)
Black	45	23	0.51 (0.28–0.93)
Asian	*	*	*
Hawaiian	*	*	*
Native American	*	*	*
Multiracial	*	*	*
Missing	153	204	1.34 (1.04–1.72)
Surgical Procedure			
Surgery/Procedure	110	145	1.35 (0.67–2.72)
No Surgery/Procedure	95	111	1.18 (1.06–1.32)
Study Year			
Study Year 2007–2012	106	124	1.18 (1.03–1.36)
Study Year 2014–2019	89	97	1.10 (0.91–1.33)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-9 Study 1b. Subgroup Results—All-Cause Mortality: Among Veterans with Current Dispensed Benzodiazepine Pharmacotherapy, Adjusted Mortality Rates and Hazard Ratios of All-Cause Mortality Between Individuals Newly Dispensed Opioid Pharmacotherapy Compared to Those Newly Dispensed Non-Opioid Pain Pharmacotherapy by Subgroups (2007–2019; $N = 319{,}990$)

All-Cause Mortality	With Current Benzodiazepine Pharmacotherapy		
	Adjusted		
	All-Cause Mortality Death Rate		Hazard ratio (CI)
Sensitivity Analysis	Newly Dispensed Non-opioid Pain Pharmacotherapy	Newly Dispensed Opioid Pharmacotherapy	
OVERALL	7,441	11,877	1.59 (1.53–1.65)
Insurance Coverage			
CMS only	15,315	34,066	2.16 (2.04–2.30)
DUAL: both VHA/CMS	3,649	4,362	1.46 (1.32–1.61)
VHA only	6,141	7,918	1.29 (1.22–1.37)
Sex			
Gender—male	7,908	12,574	1.59 (1.52–1.65)
Gender—female	2,427	3,748	1.53 (1.20–1.94)
Age ≤65+			
18–64	3,145	4,138	1.32 (1.21–1.44)
65+	12,071	21,102	1.71 (1.64–1.79)
Age (Categorical)			
18–34	1,811	1,934	1.07 (0.71–1.63)
35–54	2,281	3,049	1.35 (1.14–1.60)
55–74	4,629	6,768	1.46 (1.37–1.57)
75+	16,648	22,347	1.85 (1.77–1.94)
Ethnicity			
Hispanic (no)	7,005	11,331	1.62 (1.55–1.68)
Hispanic (yes)	4,749	6,091	1.25 (1.01–1.55)
Hispanic (missing)	7,399	80,056	10.98 (10.98–10.98)
Race			
Race (White)	7,038	11,338	1.61 (1.54–1.68)
Race (Black)	4,192	6,532	1.55 (1.28–1.88)
Race (Asian)	*	*	*
Race (Hawaiian)	5,510	8,436	1.55 (0.86–2.8)
Race (Native American)	3,602	8,895	2.52 (1.29–4.97)
Race (Multiracial)	3,536	11,461	3.46 (1.93–6.18)
Race (Missing)	11,263	26,229	1.94 (1.94–1.94)
Surgical Procedure			
Surgery/Procedure	8,054	12,054	1.48 (1.14–1.92)
No Surgery/Procedure	7,419	11,910	1.60 (1.54–1.66)
Study Year			
Study Year 2007–2012	7,273	9,797	1.36 (1.28–1.43)
Study Year 2014–2019	7,581	14,282	1.84 (1.73–1.96)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-10 Study 1b. Subgroup results—Suicide Mortality: Among Veterans With Current Dispensed Benzodiazepine Pharmacotherapy, Adjusted Mortality Rates and Hazard Ratios of Suicide Mortality Between Individuals Newly Dispensed Opioid Pharmacotherapy Compared to Those Newly Dispensed Non-Opioid Pain Pharmacotherapy by Subgroups (2007–2019; *N* = 319,990)

Suicide Mortality	**With Current Benzodiazepine Pharmacotherapy**		
	Adjusted		
	Suicide Mortality Death Rate		
Sensitivity Analysis	**Newly Dispensed Non-opioid Pain Pharmacotherapy**	**Newly Dispensed Opioid Pharmacotherapy**	**Hazard ratio**
OVERALL	238	246	1.03 (0.81–1.31)
Insurance Coverage			
CMS only	213	261	1.20 (0.68–2.13)
DUAL: both VHA/CMS	*	*	*
VHA only	274	268	0.98 (0.73–1.32)
Sex			
Gender—male	239	243	1.01 (0.78–1.30)
Gender—female	*	*	*
Age ≤65+			
18–64	286	306	1.08 (0.79–1.46)
65+	183	208	1.11 (0.75–1.64)
Age (Categorical)			
18–34	*	*	*
35–54	310	399	1.28 (0.8–2.04)
55–74	209	166	0.79 (0.53–1.18)
75+	186	184	1.31 (0.83–2.07)
Ethnicity			
Hispanic (no)	251	240	0.95 (0.73–1.24)
Hispanic (yes)	*	*	*
Hispanic (missing)	0	0	0.11 (0.04–0.32)
Race			
Race (White)	241	258	1.07 (0.82–1.40)
Race (Black)	*	*	*
Race (Asian)	*	*	*
Race (Hawaiian)	*	*	*
Race (Native American)	*	*	*
Race (Multiracial)	*	*	*
Race (Missing)	0	0	Failed to converge
Surgical Procedure			
Surgery/Procedure	*	*	*
No Surgery/Procedure	232	246	1.05 (0.82–1.35)
Study Year			
Study Year 2007–2012	295	268	0.91 (0.67–1.24)
Study Year 2014–2019	181	213	1.15 (0.72–1.84)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

already taking benzodiazepines. To respond to the statement of task, especially (d), the study population was stratified into two groups: those without a current benzodiazepine pharmacotherapy and those with a current benzodiazepine pharmacotherapy.

All-Cause Mortality and Suicide Mortality

Findings for all-cause mortality was consistent across the ITT and per protocol analyses.

These findings align with research among the general population demonstrating that long-term use of opioid pharmacotherapy is linked to medical conditions that may lead to death, including respiratory conditions (Ray et al., 2016), cardiovascular events (Sung et al., 2024), adverse effects on gastrointestinal, endocrine, and immunologic systems (Chou et al., 2015; Khansari et al., 2013; Leppert, 2012; Brack et al., 2011), opioid addiction, and overdose death. Non-VA studies have indicated that a proportion of opioid-naïve individuals who receive opioid pharmacotherapy for acute pain treatment or post-surgery pain management may be prescribed long-term opioid pharmacotherapy (Brummett et al., 2017; Kyriacou, 2017; Deyo et al., 2017; Shah et al., 2017). Similarly, veterans often initiate use of opioid medications due to service-related injuries (Kelber et al., 2022; Golub and Bennett, 2013).

As detailed in chapters 1 and 6, outcomes such as all-cause mortality, deaths to accidents, suicide, and overdose, regardless of misuse, are associated with concurrent long-term opioid pharmacotherapy and benzodiazepine pharmacotherapy (VA/DoD, 2022; Gibbons et al., 2021; Xu et al., 2020; Bohnert and Ilgen, 2019; Gressler et al., 2018; Sun et al., 2017; VA/DoD, 2017; Park et al., 2015). Since veterans disproportionately experience both physical and psychological trauma, many receive treatment for both chronic pain and mental health conditions, increasing the likelihood of concurrent use of opioid and benzodiazepine pharmacotherapies (NASEM, 2018). In addition to the ongoing efforts of VHA to address the opioid crisis discussed (e.g., updating the CPGs), prescription drug monitoring programs could be useful tools for providers to avoid prescribing opioid pharmacotherapy to veterans already prescribed benzodiazepine pharmacotherapy. This is crucial because veterans can receive prescriptions from multiple providers (e.g., across the VHA, Medicare, and private insurance).[14]

Consistent across the ITT and per protocol analyses, findings show that among veterans without current benzodiazepine pharmacotherapy (study 1a), individuals newly dispensed opioid (versus non-opioid pain) pharmacotherapy had an increased risk of suicide mortality. For veterans with currently dispensed benzodiazepine pharmacotherapy (study 1b), the 1.03 for suicide mortality and imprecision resulted in inconclusive findings. Research has identified an association of all-cause mortality in the veteran population with incident fills of opioid pharmacotherapy and benzodiazepine pharmacotherapies in the Veteran Aging Cohort Study (Gaither et al., 2016, Weisberg et al., 2015) and veterans with PTSD (Hawkins et al., 2023). Consistent findings for all-cause mortality were identified across studies with different comparison groups (e.g., no analgesic use versus opioid-only versus non-opioid pain pharmacotherapy as a comparison), criteria for a opioid fill (e.g., >90 days, ≥7 days) and a benzodiazepine fill (e.g., ≥7 days, >5 tablets), proxy definitions for overlapping use of an opioid and benzodiazepine through fill data (e.g., co-prescription, overlap of ≥30 days, or ≥90 days of either medication at any point over a 12-month period, fill within a 30-day time window), and study designs (e.g., none using a target emulated trial) (Hawkins et al., 2023, Gaither et al., 2016, Weisberg et al., 2015). Hawkins and colleagues (2023) identified an increase in all-cause mortality in the concomitant opioid and benzodiazepine pharmacotherapy group when compared to monotherapy (opioid pharmacotherapy alone; benzodiazepine pharmacotherapy alone), but no association was identified for death due to circulatory or respiratory causes. This suggests that factors not related to non-opioid pharmacotherapy are the cause of death and that these individuals have an increased risk of death due to factors not able to be extracted using diagnostic or procedure codes (Hawkins et al., 2023). While combined use may be appropriately prescribed in select scenarios (Boon et al., 2020, Gaither et al., 2016), this should be done with caution (FDA, 2016).

The committee's findings should not be interpreted as clinical guidance on the combined use of opioid and benzodiazepine pharmacotherapy in veterans or those at risk for suicide. First, the statement of task did not specify a focus on veterans at risk for suicide and, thus, this was not the population studied. Second, individuals at risk

[14] Public Law 113-146, Veterans Access, Choice and Accountability Act of 2014, 113th Congress, August 7, 2014.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

for suicide may have an increased risk for an intentional overdose. Third, drug–drug interactions are well established, increasing the risk of respiratory depression in overdose situations (see previous discussion) when opioid pharmacotherapy is combined with benzodiazepine pharmacotherapy.

The committee evaluated the results based on several Bradford Hill criteria: biological plausibility, consistency of the association, time sequence, specificity, strength of the association, study design, quantitative strength, and dose response (Hill, 1965).

It is biologically plausible that opioid and benzodiazepine pharmacotherapy, either alone or together, can lead to the study outcomes through respiratory depression, which can cause hypoxia, hypercapnia cardiorespiratory arrest, and eventually death (Baldo, 2021; Forster et al., 1983). Further, the study design follows individuals from their start date or entry into the study, based on their treatment group, and observes them over 12 months or until the outcome of interest, all-cause mortality or suicide mortality, occurs.

The results are consistent with other studies, as mentioned above (Boon et al., 2020; Gaither et al., 2016; Weisberg et al., 2015). Specificity could not be assessed in this study, since the committee did not exhaustively assess all available pharmacological and non-pharmacological pain treatments, or all potential outcomes associated with pain pharmacotherapy (Fedak et al., 2015).

The strength of the association is based on quantitative strength, study design, and dose response. In study 1a (without current dispensed benzodiazepine pharmacotherapy), the adjusted HR for all-cause mortality was 1.61 (95% CI: 1.59–1.63) in those newly dispensed opioid pharmacotherapy, compared to those newly dispensed non-opioid pain pharmacotherapy. In Study 1b (with current dispensed benzodiazepine pharmacotherapy), the adjusted HR for all-cause mortality was 1.59 (95% CI: 1.53–1.65). As for the study design, the committee applied the TTE framework, reflecting current best practices in the causal inference methodology field when using observational data. The design reduced confounders and biases inherent in observational studies.

These findings are consistent with guidelines indicating avoidance of concurrent use of opioid and benzodiazepine pharmacotherapy (VA/DoD, 2022, 2017; Dowell et al., 2016; FDA, 2016). In addition, guidelines recommending against concurrent use are complemented by the decrease of co-prescribing in recent years—from 31.2 per 100 persons in 2017 to 25.8 per 100 persons in 2021.[15] It is important to note that the committee's interpretation of the results is not intended to influence restriction for any medication nor is not to be viewed as an absolute contraindication for the clinical use of benzodiazepines with opioids.

Strengths and Limitations

This study has important strengths. First, the committee used all VHA data available from 2007 to 2019, and Medicare and NDI data, incorporating as much information as possible for the analysis. Second, to enhance the validity of the inferences, the committee's approach followed current best practices, including the use of a TTE framework, comparison of clinically realistic treatment strategies, avoidance of biases related to mishandling time zero, and rigorous adjustment for baseline and time-varying confounding. Other strengths including leveraging the VA dataset, spanning several years, to yield a sample of nearly 6 million individuals reflected in the analysis.

However, the findings should be interpreted with caution due to a few limitations. First, the study relied on health care clinical and administrative data, which may not capture the use of pain medications obtained illicitly outside health care settings. Additionally, pharmacy data were limited to prescriptions covered by the VHA and Medicare Part D, and thus the committee was not able to incorporate those covered by other sources (e.g., private, Medicaid, TRICARE, self-pay). In addition, there could be underreporting of medications, such as acetaminophen. The data does not include acetaminophen obtained via over the counter, and only reflect prescribed acetaminophen. Thus, under reporting may occur. Second, the committee did not require a chronic pain diagnosis as an inclusion criterion because it may be underdiagnosed and not reflected in EHR or be in the EHR but not identifiable as being chronically painful (e.g., osteoarthritis, low back pain, non-organized signs and symptoms). Third, the study faced challenges in fully capturing and identifying suicide mortality due to the specificity issues of certain ICD-10 suicide codes. Fourth, analyses were not able to incorporate veteran history of opioid pharmacotherapy exposure, especially

[15] Dr. Christopher Jones, presentation to the committee on March 9, 2023. Trends in Opioid and Benzodiazepine Use, Misuse, and Overdose.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

prescriptions prior to the episode of interest; before the washout period; during active duty, previous long-term care, or hospitalizations; or in the private sector (with the exception of Medicare Part D). The committee also did not have any information regarding previous use and failure of opioid and non-opioid pain pharmacotherapy, including a failure in providing adequate pain relief. Fifth, although the committee used a follow-up period of 12 months, it is unclear whether this was long enough. Sixth, the studies did not examine the potential indirect effects of substance use or naloxone administration. Seventh, given the statement of task, the committee did not assess non-pharmacologic treatments for pain (e.g., physical therapy, acupuncture, or chiropractic care), which are included VA benefits and have been increasing in utilization in recent years. There is growing evidence of the opioid sparing effects of some of these treatment approaches. Eighth, the committee examined covariate balance proximal to the index period; although covariate status 365 days prior the index period would be an interesting factor to explore, ICD diagnostic codes do not usually coincide with the incident date of the disease, potentially introducing a bias. The subgroup analysis did include adjustment based on surgical procedure; but resulted in no difference in the outcome between the two treatment groups. Finally, the findings may not be generalizable to civilians or veterans who receive care outside VHA. Additional details on study limitations can be found in Chapter 3.

FINDINGS

The committee was tasked with quantifying the effects of opioid and benzodiazepine pharmacotherapy prescribing on the risk of death among veterans who received care from the VHA between 2007–2019. Study 1 addresses the objectives outlined in parts (a) and (d) of the committee's statement of task. Specifically, the study focused on (a) the effect of opioid prescribing for pain compared to alternative non-opioid pain treatments and (d) the effect of initiating opioids in individuals who are already taking benzodiazepines. These findings were consistent across both ITT and per protocol analyses and various subgroups. The committee cannot distinguish between the effect of opioid pharmacotherapy and the reason it was dispensed.

Finding 1a-1. Among veterans without current benzodiazepine pharmacotherapy, the 12-month risk of all-cause mortality was 10,273 deaths per 100,000 person-years for those newly dispensed opioid pharmacotherapy and 6,473 deaths per 100,000 person-years for those newly dispensed non-opioid pain pharmacotherapy (aHR[16]: 1.61; 95% CI: 1.59–1.63).

Finding 1a-2. Among veterans without current benzodiazepine pharmacotherapy, the 12-month risk for suicide mortality was 112 deaths per 100,000 person-years for those newly dispensed opioid pharmacotherapy and 95 deaths per 100,000 person-years for those newly dispensed non-opioid pain pharmacotherapy (aHR: 1.19; 95% CI: 1.07–1.32).

Finding 1b-1. Among veterans with current benzodiazepine pharmacotherapy, the 12-month risk for all-cause mortality was 11,877 deaths per 100,000 person-years for those newly dispensed opioid pharmacotherapy and 7,441 deaths per 100,000 person-years for those newly dispensed non-opioid pain pharmacotherapy (aHR: 1.59; 95% CI: 1.53–1.65).

Finding 1b-2. Among veterans with current benzodiazepine pharmacotherapy, the 12-month risk for suicide mortality was 246 deaths per 100,000 person-years for those newly dispensed opioid pharmacotherapy and 238 deaths per 100,000 person-years for those newly dispensed non-opioid pain pharmacotherapy, (aHR: 1.03; 95% CI: 0.81–1.31).

[16] aHR: adjusted hazard ratio

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

CONCLUSIONS

The committee evaluated the effect of newly dispensed opioid pharmacotherapy without and with concurrent benzodiazepine pharmacotherapy on all-cause mortality and suicide mortality. The committee employed the TTE framework to reduce biases, such as due to immortal time, and confounding. In addition, the committee leveraged the large observational datasets (e.g., health care, clinical, and administrative data) available within the VA and VHA, supplemented by CMS data, and the NDI for mortality data. Based on the study findings, the committee makes the following conclusions for veterans who received care from the VHA between 2007–2019:

Conclusion 1. The committee concludes that there is an increased risk of all-cause mortality among veterans newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy.

Conclusion 2. The committee concludes that there is an increased risk of all-cause mortality among veterans co-prescribed opioid and benzodiazepine pharmacotherapies compared to those co-prescribed non-opioid pain and benzodiazepine pharmacotherapies.

Conclusion 5. The committee concludes that there is an increased risk of suicide mortality among veterans newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy.

Conclusion 6. The committee concludes there is no evidence of a difference in the risk of suicide mortality among veterans newly dispensed opioid pharmacotherapy and currently dispensed benzodiazepine pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy and currently dispensed benzodiazepine pharmacotherapy.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

ANNEX: SUPPLEMENTARY FIGURES AND TABLES

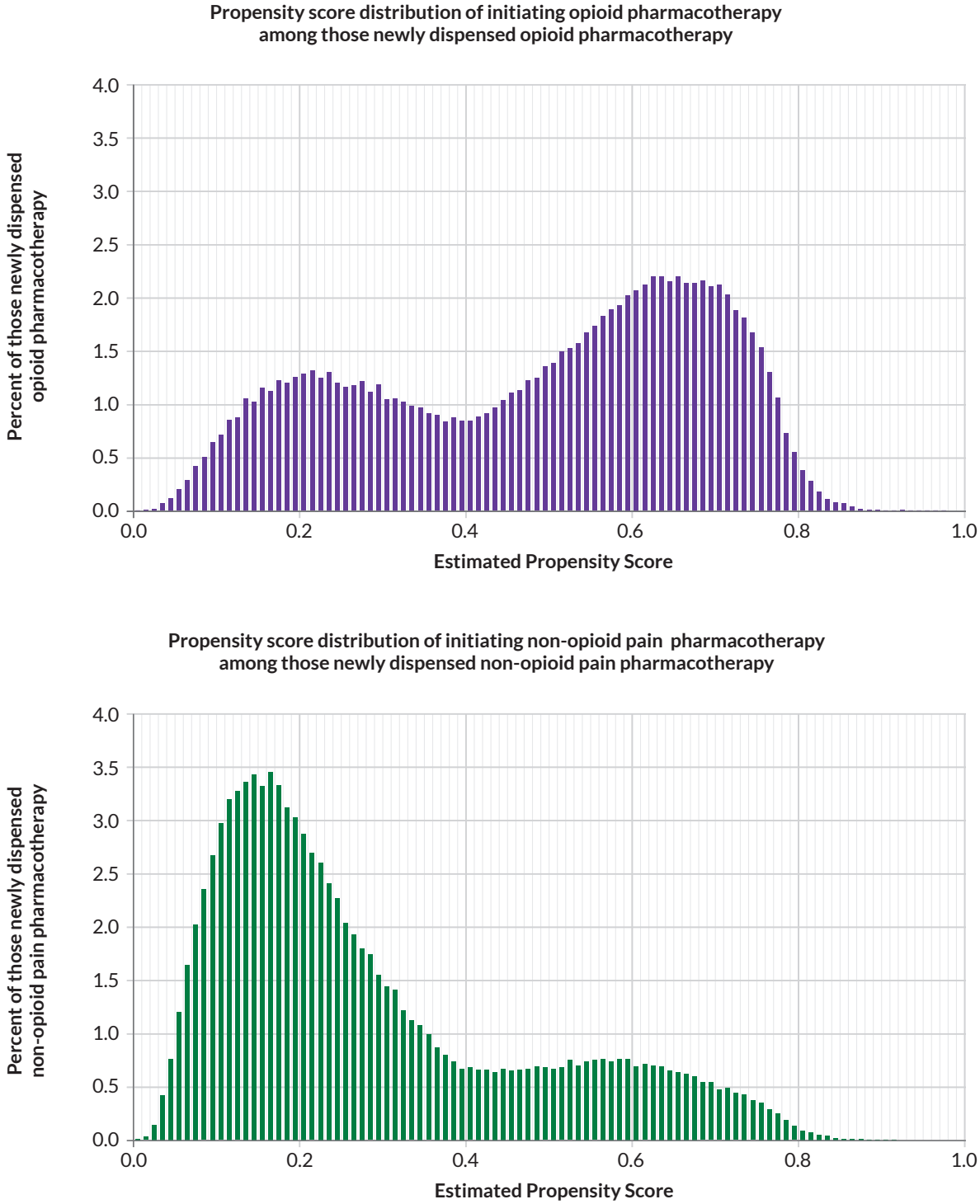

FIGURE 4-5 Study 1a. Among veterans without a current benzodiazepine pharmacotherapy, propensity score distribution of initiating opioid pharmacotherapy among those newly dispensed opioid pharmacotherapy (top panel) and those newly dispensed non-opioid pain pharmacotherapy (bottom panel) (2007–2019; $N = 5{,}636{,}207$).
NOTE: No cells are reported representing 10 or fewer veterans.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

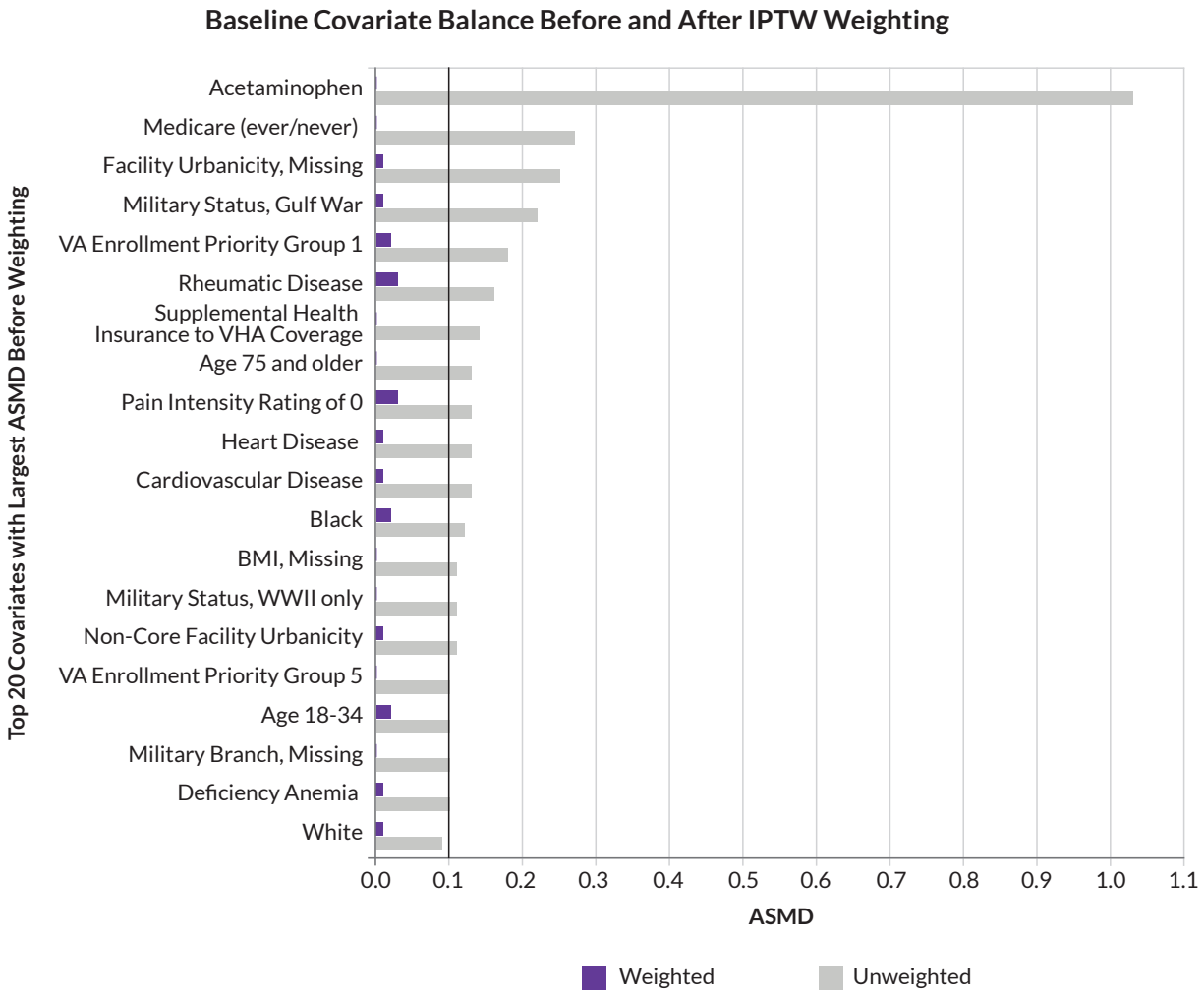

FIGURE 4-6 Study 1a. Among veterans without current benzodiazepine pharmacotherapy, baseline covariate balance between those newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy before and after inverse probability treatment weighting (2007–2019; $N = 5{,}636{,}207$).
NOTES: No cells are reported representing 10 or fewer veterans. Only the 20 covariates with the greatest magnitude of change presented in figure

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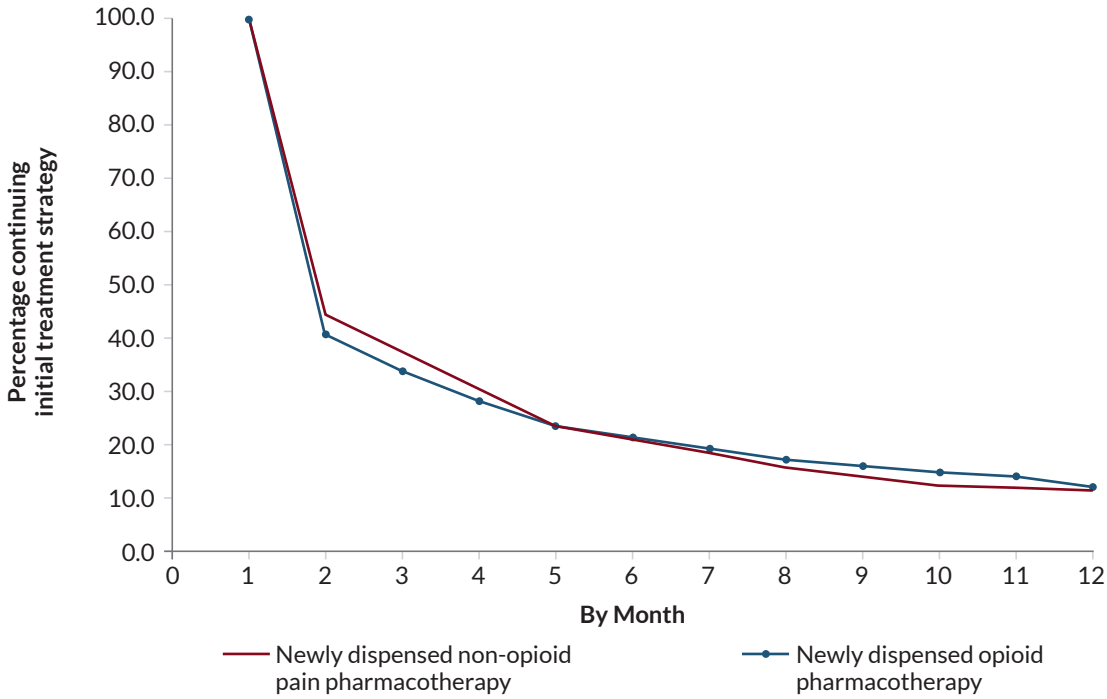

FIGURE 4-7 Study 1a. Time to discontinuation. Among veterans without current benzodiazepine pharmacotherapy, time to discontinuation of pharmacotherapy in those newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy (2007–2019; *N*=5,636,207).
NOTE: No cells are reported representing 10 or fewer veterans.

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TABLE 4-11 Study 1a. Missing Percentages of Variables in the Model. Among Those Without Current Benzodiazepine Pharmacotherapy, Missingness of Variables Included in the Current Analysis by Total, Those Newly Dispensed Opioid Pharmacotherapy, and Those Newly Dispensed Non-Opioid Pain Pharmacotherapy (2007–2019; N = 5,636,207)

Covariate	Total (%)	Newly Dispensed Opioid Pharmacotherapy (%)	Newly Dispensed Non-Opioid Pain Pharmacotherapy (%)
Sex	0.00	0.00	0.00
Age	0.00	0.00	0.00
Race	9.86	9.74	9.91
Ethnicity	6.03	5.95	6.06
Marital Status	5.23	5.29	5.20
Disability Status	0.31	0.31	0.31
History of homelessness	0.00	0.00	0.00
Tobacco Use Ever	0.00	0.00	0.00
Health Conditions			
Physical Health Conditions			
Acute Pain Injury	0.00	0.00	0.00
AIDS/HIV	0.00	0.00	0.00
Blood Loss Anemia	0.00	0.00	0.00
Cancer (non-melanoma skin)	0.00	0.00	0.00
Cardiovascular Disease	0.00	0.00	0.00
Cerebrovascular Disease	0.00	0.00	0.00
Chronic Lung Disease	0.00	0.00	0.00
Cirrhosis	0.00	0.00	0.00
COPD[1]	0.00	0.00	0.00
Deficiency Anemia	0.00	0.00	0.00
Dementia	0.00	0.00	0.00
Diabetes	0.00	0.00	0.00
End-Stage Renal Disease	0.00	0.00	0.00
Heart Disease	0.00	0.00	0.00
Hepatitis	0.00	0.00	0.00
Hemiplegia or Paraplegia	0.00	0.00	0.00
Liver Disease	0.00	0.00	0.00
Migraine	0.00	0.00	0.00
Peptic Ulcer Disease	0.00	0.00	0.00
Peripheral Vascular Disease	0.00	0.00	0.00
Pulmonary Circulation Disorders	0.00	0.00	0.00
Rheumatic Disease	0.00	0.00	0.00
Syncope	0.00	0.00	0.00
Sleep Disorders			
Apnea	0.00	0.00	0.00
Insomnia	0.00	0.00	0.00

continued

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TABLE 4-11 Continued

Covariate	Total (%)	Newly Dispensed Opioid Pharmacotherapy (%)	Newly Dispensed Non-Opioid Pain Pharmacotherapy (%)
Mental Health			
ADHD[2]	0.00	0.00	0.00
Alcohol Use Disorder	0.00	0.00	0.00
Anxiety	0.00	0.00	0.00
Bipolar Disorder	0.00	0.00	0.00
Depression	0.00	0.00	0.00
Drug Use Disorder	0.00	0.00	0.00
Opioid Use Disorder	0.00	0.00	0.00
Posttraumatic Stress Disorder	0.00	0.00	0.00
Schizophrenia and Psychosis	0.00	0.00	0.00
Suicidal Ideation	0.00	0.00	0.00
Traumatic Brain Injury	0.00	0.00	0.00
Overdose-Related Diagnoses			
Opioid overdose	0.00	0.00	0.00
Current Pain Intensity Rating	17.09	16.98	17.14
Body Mass Index	9.27	9.19	9.31
Health Care Coverage			
Supplemental Health Insurance to VHA[3] Coverage			
Medicare (ever/never)	0.00	0.00	0.00
Health Care Utilization in Past Year			
Number of VA Outpatient Visits	0.00	0.00	0.00
Inpatient Hospital Admission	0.00	0.00	0.00
Inpatient Procedure	0.00	0.00	0.00
Inpatient Surgery	0.00	0.00	0.00
Outpatient Procedure	0.00	0.00	0.00
Nursing Home Visit	0.00	0.00	0.00
Military Status			
Service Era	1.72	1.70	1.73
Combat Service	13.48	13.20	13.59
Military Sexual Trauma	2.18	2.16	2.19
Military Branch	16.35	16.26	16.38
Prescription Information (Yes/No)			
Anticonvulsant	0.00	0.00	0.00
Antihistamine	0.00	0.00	0.00
Anxiolytic	0.00	0.00	0.00
Buprenorphine (for pain)	0.00	0.00	0.00
Migraine	0.00	0.00	0.00
Acetaminophen	0.00	0.00	0.00

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-11 Continued

Covariate	Total (%)	Newly Dispensed Opioid Pharmacotherapy (%)	Newly Dispensed Non-Opioid Pain Pharmacotherapy (%)
SNRI[4]	0.00	0.00	0.00
TeCA[5]	0.00	0.00	0.00
Facility Urbanicity	13.67	13.86	13.58

[1] COPD: Chronic obstructive pulmonary disease.
[2] ADHD: Attention-deficit/hyperactivity disorder.
[3] VHA: Veteran Health Affairs.
[4] SNRI: Serotonin-norepinephrine reuptake inhibitor.
[5] TeCA: Tetracyclic antidepressant.
NOTE: No cells are reported representing 10 or fewer veterans.

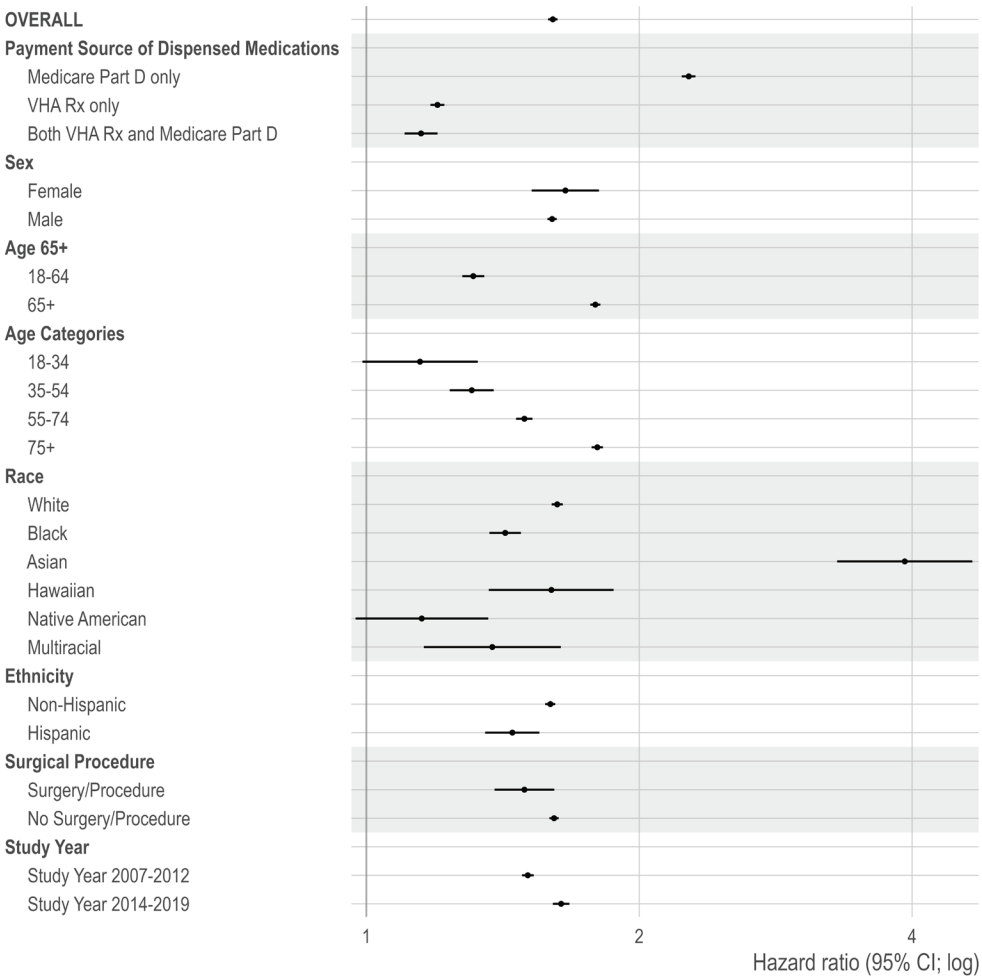

FIGURE 4-8 Study 1a. Among those without current benzodiazepine pharmacotherapy, the adjusted hazard ratios of all-cause mortality between veterans newly dispensed opioid pharmacotherapy versus veterans newly dispensed non-opioid pain pharmacotherapy by subgroups (forest plots).
NOTE: No cells are reported representing 10 or fewer veterans.

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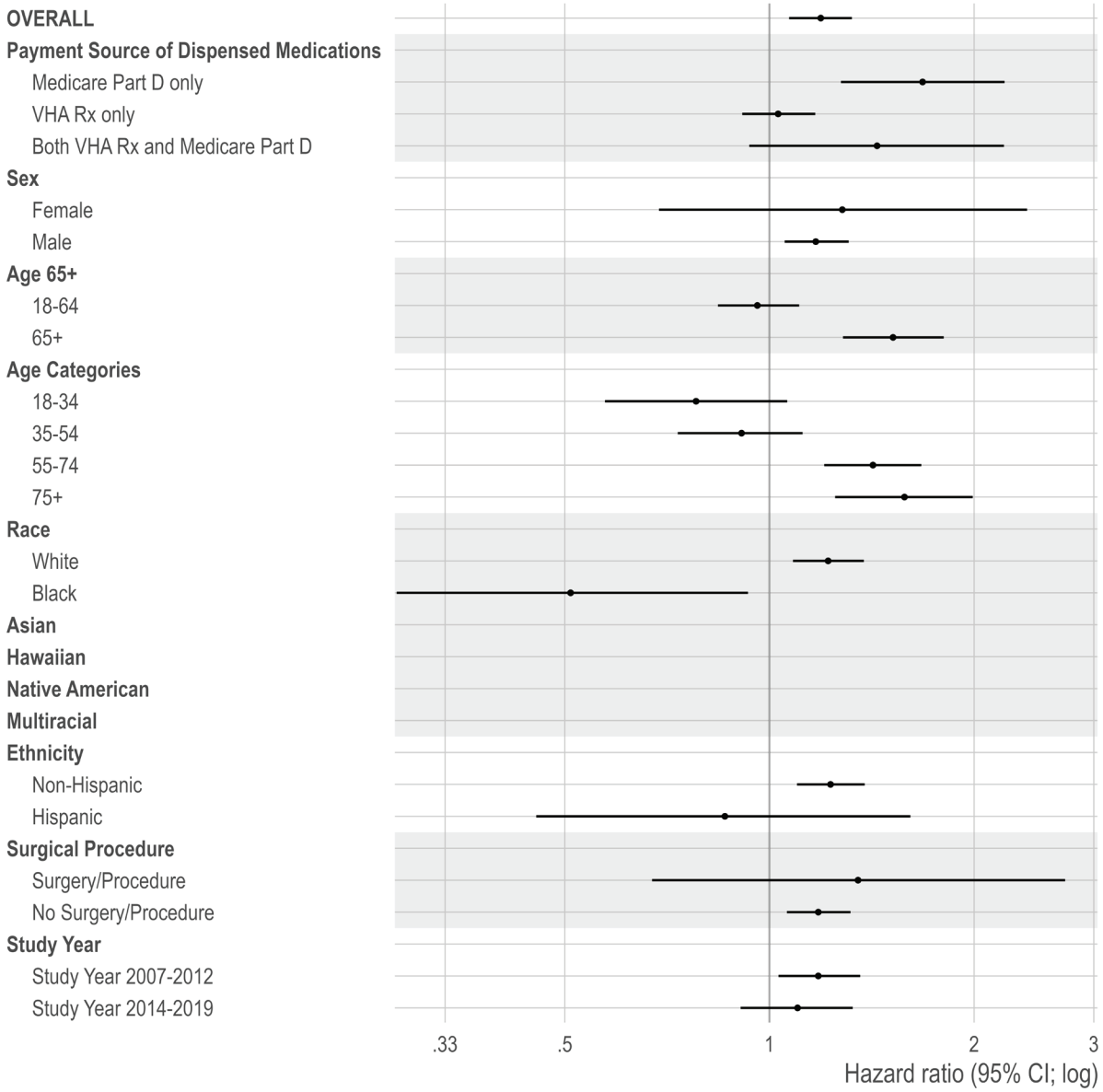

FIGURE 4-9 Study 1a. Among those without current benzodiazepine pharmacotherapy, the adjusted hazard ratios of suicide mortality between veterans with newly dispensed opioid pharmacotherapy versus veterans with non-opioid pain pharmacotherapy subgroups (forest plots).
NOTE: No cells are reported representing 10 or fewer veterans.

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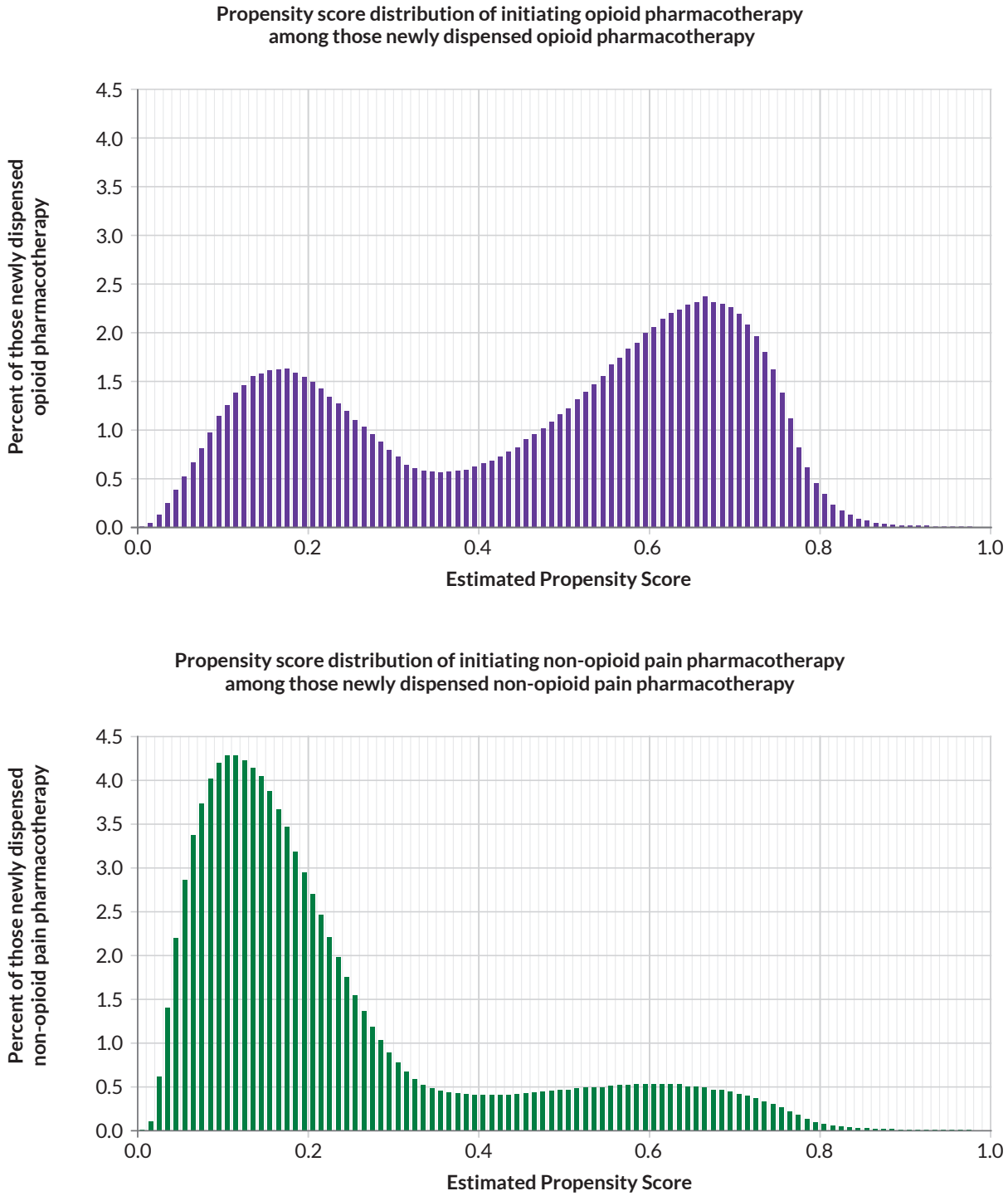

FIGURE 4-10 Study 1b. Among veterans with current benzodiazepine pharmacotherapy, propensity score distribution of newly dispensed opioid pharmacotherapy among those newly dispensed opioid pharmacotherapy (top panel) and those newly dispensed non-opioid pain pharmacotherapy (bottom panel) (2007–2019; $N = 319{,}990$).
NOTE: No cells are reported representing 10 or fewer veterans.

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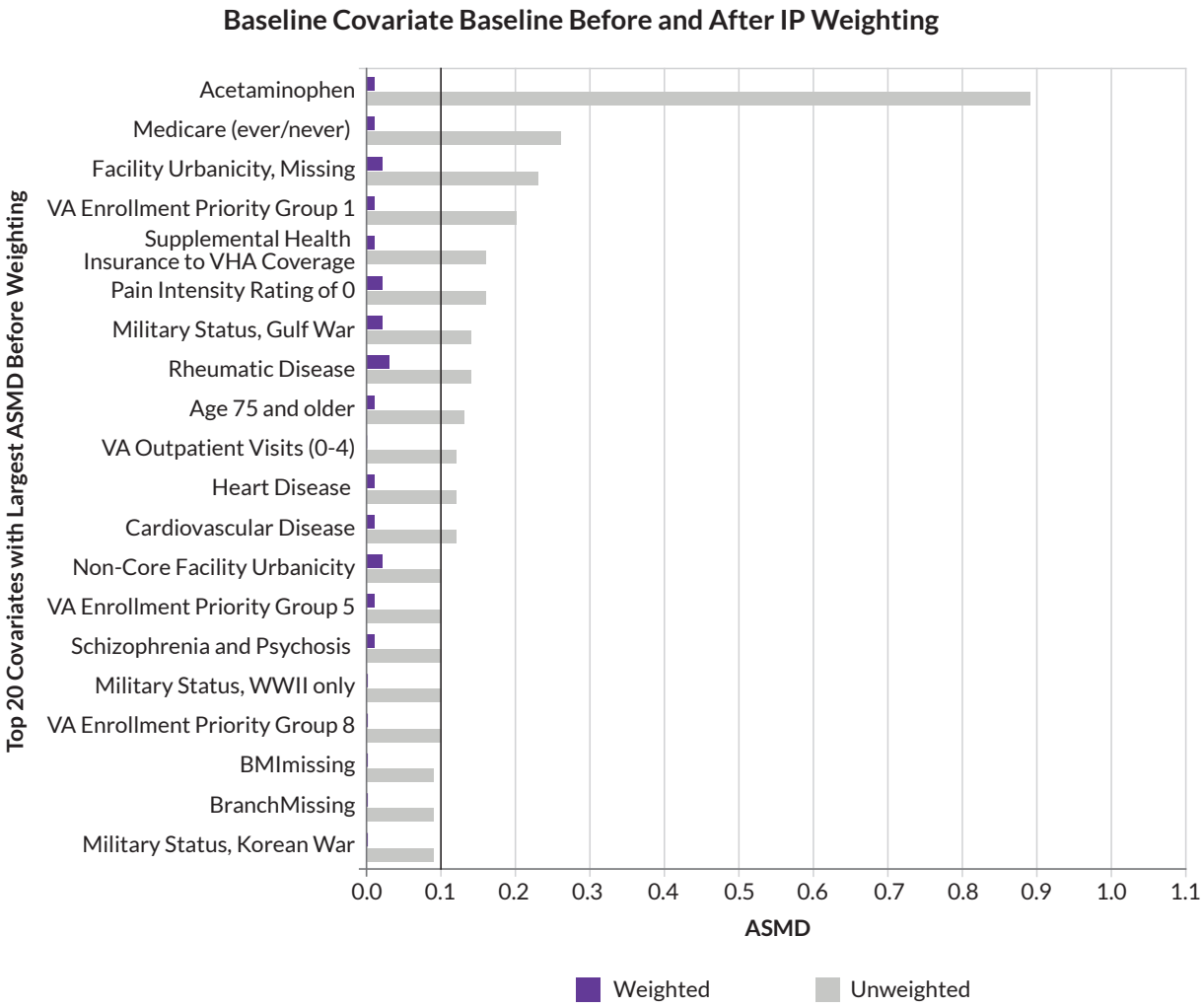

FIGURE 4-11 Study 1b. Among veterans with a current dispensed benzodiazepine pharmacotherapy, baseline covariate balance between those newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pain pharmacotherapy before and after inverse probability treatment weighting (2007–2019; N = 319,990).
NOTES: No cells are reported representing 10 or fewer veterans. ASMD = absolute standardize mean difference; IP = inverse probability.

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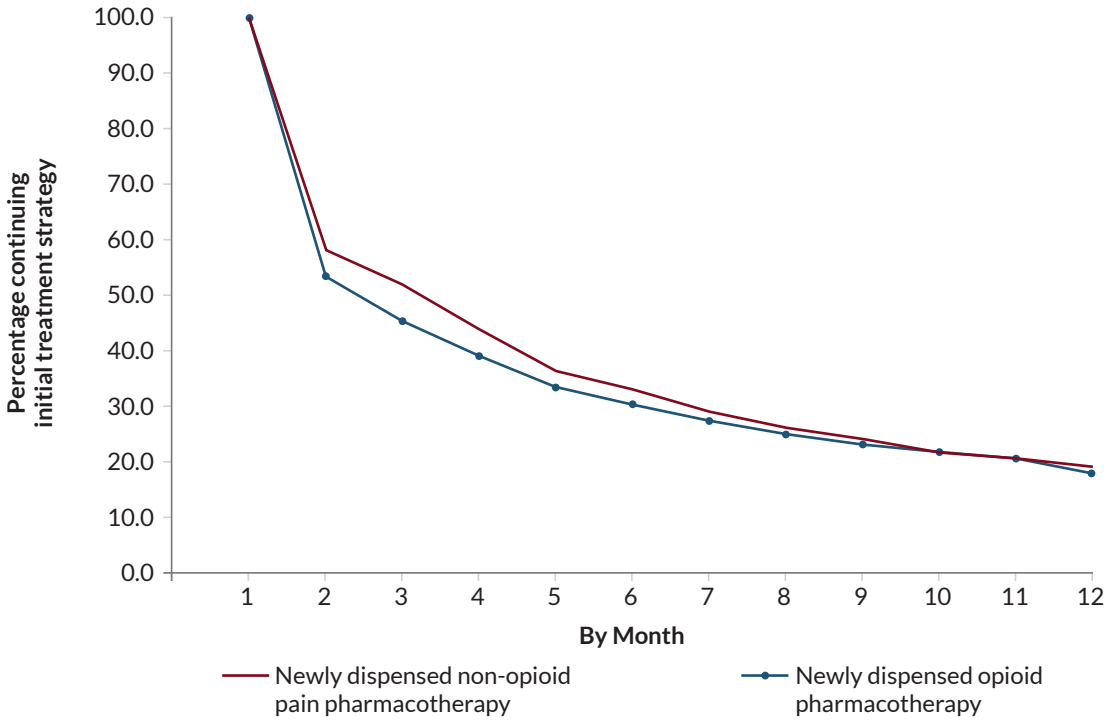

FIGURE 4-12 Study 1b. Time to discontinuation. Among veterans with a current dispensed benzodiazepine pharmacotherapy, time to discontinuation of treatment in those newly dispensed opioid pharmacotherapy compared to those newly dispensed non-opioid pharmacotherapy (2007–2019; $N = 319{,}990$).
NOTES: Censored at veteran-month for first month of continuous 3 months of non-adherence, new cancer diagnosis, new palliative care/hospice ICD code in medical record. No cells are reported representing 10 or fewer veterans.

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TABLE 4-12 Study 1b. Missing Percentages of Variables in the Model. Among Those with a Current Dispensed Benzodiazepine Pharmacotherapy, Missingness of Variables Included in the Current Analysis by Total, Those Newly Dispensed Opioid Pharmacotherapy, and Those Newly Dispensed Non-Opioid Pain Pharmacotherapy (2007–2019; *N* = 319,990)

Covariate	Total (%)	Newly Dispensed Opioid Pharmacotherapy (%)	Newly Dispensed Non-Opioid Pain Pharmacotherapy (%)
Sex	0.00	0.00	0.00
Age	0.00	0.00	0.00
Race	9.97	9.97	9.98
Ethnicity	5.97	5.97	5.97
Marital Status	5.99	6.13	5.92
Disability Status	0.19	0.19	0.19
History of homelessness	0.00	0.00	0.00
Tobacco Use Ever	0.00	0.00	0.00
Health Conditions			
Physical Health Conditions			
Acute Pain Injury	0.00	0.00	0.00
AIDS/HIV	0.00	0.00	0.00
Blood Loss Anemia	0.00	0.00	0.00
Cancer (non-melanoma skin)	0.00	0.00	0.00
Cardiovascular Disease	0.00	0.00	0.00
Cerebrovascular Disease	0.00	0.00	0.00
Chronic Lung Disease	0.00	0.00	0.00
Cirrhosis	0.00	0.00	0.00
COPD[1]	0.00	0.00	0.00
Deficiency Anemia	0.00	0.00	0.00
Dementia	0.00	0.00	0.00
Diabetes	0.00	0.00	0.00
End-Stage Renal Disease	0.00	0.00	0.00
Heart Disease	0.00	0.00	0.00
Hepatitis	0.00	0.00	0.00
Hemiplegia or Paraplegia	0.00	0.00	0.00
Liver Disease	0.00	0.00	0.00
Migraine	0.00	0.00	0.00
Peptic Ulcer Disease	0.00	0.00	0.00
Peripheral Vascular Disease	0.00	0.00	0.00
Pulmonary Circulation Disorders	0.00	0.00	0.00
Rheumatic Disease	0.00	0.00	0.00
Syncope	0.00	0.00	0.00
Sleep Disorders			
Apnea	0.00	0.00	0.00
Insomnia	0.00	0.00	0.00

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-12 Continued

Covariate	Total (%)	Newly Dispensed Opioid Pharmacotherapy (%)	Newly Dispensed Non-Opioid Pain Pharmacotherapy (%)
Mental Health			
Attention-Deficit/Hyperactivity Disorder	0.00	0.00	0.00
Alcohol Use Disorder	0.00	0.00	0.00
Anxiety	0.00	0.00	0.00
Bipolar Disorder	0.00	0.00	0.00
Depression	0.00	0.00	0.00
Drug Use Disorder	0.00	0.00	0.00
Opioid Use Disorder	0.00	0.00	0.00
Posttraumatic Stress Disorder	0.00	0.00	0.00
Schizophrenia and Psychosis	0.00	0.00	0.00
Suicidal Ideation	0.00	0.00	0.00
Traumatic Brain Injury	0.00	0.00	0.00
Overdose-Related Diagnoses			
Opioid overdose	0.00	0.00	0.00
Current Pain Intensity Rating	18.67	18.64	18.68
Body Mass Index	8.27	8.24	8.29
Health Care Coverage			
Supplemental Health Insurance to VHA[2] Coverage			
Medicare (ever/never)	0.00	0.00	0.00
Health Care Utilization in Past Year			
Number of VA Outpatient Visits	0.00	0.00	0.00
Inpatient Hospital Admission	0.00	0.00	0.00
Inpatient Procedure	0.00	0.00	0.00
Inpatient Surgery	0.00	0.00	0.00
Outpatient Procedure	0.00	0.00	0.00
Nursing Home Visit	0.00	0.00	0.00
Military Status			
Service Era	1.84	1.85	1.84
Combat Service	9.49	9.45	9.51
Military Sexual Trauma	2.03	2.06	2.02
Military Branch	16.86	16.84	16.88
Prescription Information (Rx[2] Taken) During Follow-Up, Yes/No)			
Anticonvulsants	0.00	0.00	0.00
Antihistamine	0.00	0.00	0.00
Anxiolytic	0.00	0.00	0.00
Buprenorphine (for pain)	0.00	0.00	0.00
Migraine	0.00	0.00	0.00

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 4-12 Continued

Covariate	Total (%)	Newly Dispensed Opioid Pharmacotherapy (%)	Newly Dispensed Non-Opioid Pain Pharmacotherapy (%)
Acetaminophen	0.00	0.00	0.00
SNRI[4]	0.00	0.00	0.00
TeCA[5]	0.00	0.00	0.00
Facility Urbanicity	19.29	19.70	19.07

[1] COPD: Chronic obstructive pulmonary disease.
[2] VHA: Veteran Health Affairs.
[3] Rx: Prescription.
[4] SNRI: Serotonin-norepinephrine reuptake inhibitor.
[5] TeCA: Tetracyclic antidepressant.
NOTE: No cells are reported representing 10 or fewer veterans.

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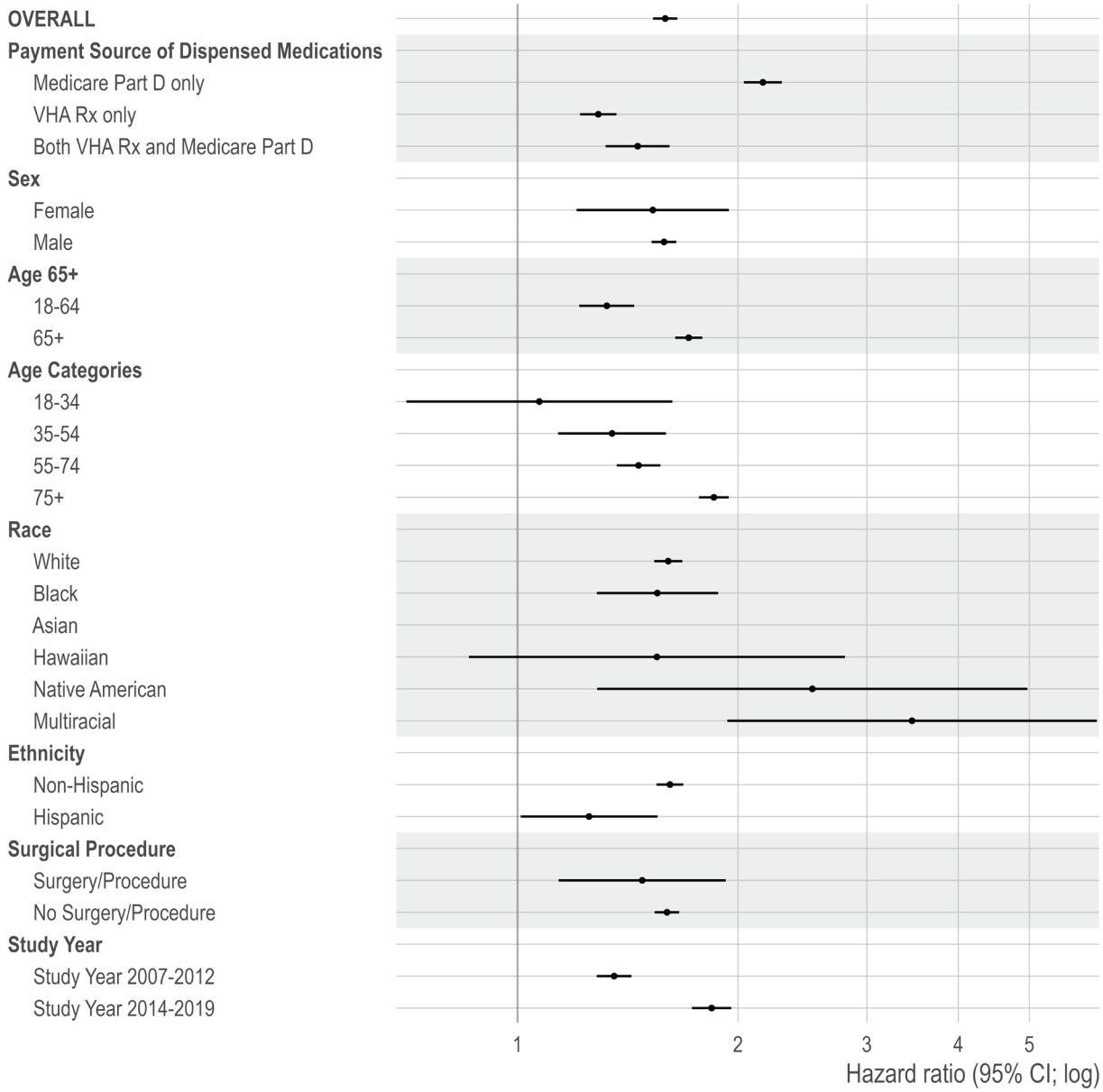

FIGURE 4-13 Study 1b. Among those with a current dispensed benzodiazepine pharmacotherapy, adjusted hazard ratios of all-cause mortality between newly dispensed opioid pharmacotherapy versus non-opioid pain pharmacotherapy by subgroups, 2007–2019; $N = 319{,}990$) (forest plots).
NOTE: No cells are reported representing 10 or fewer veterans.

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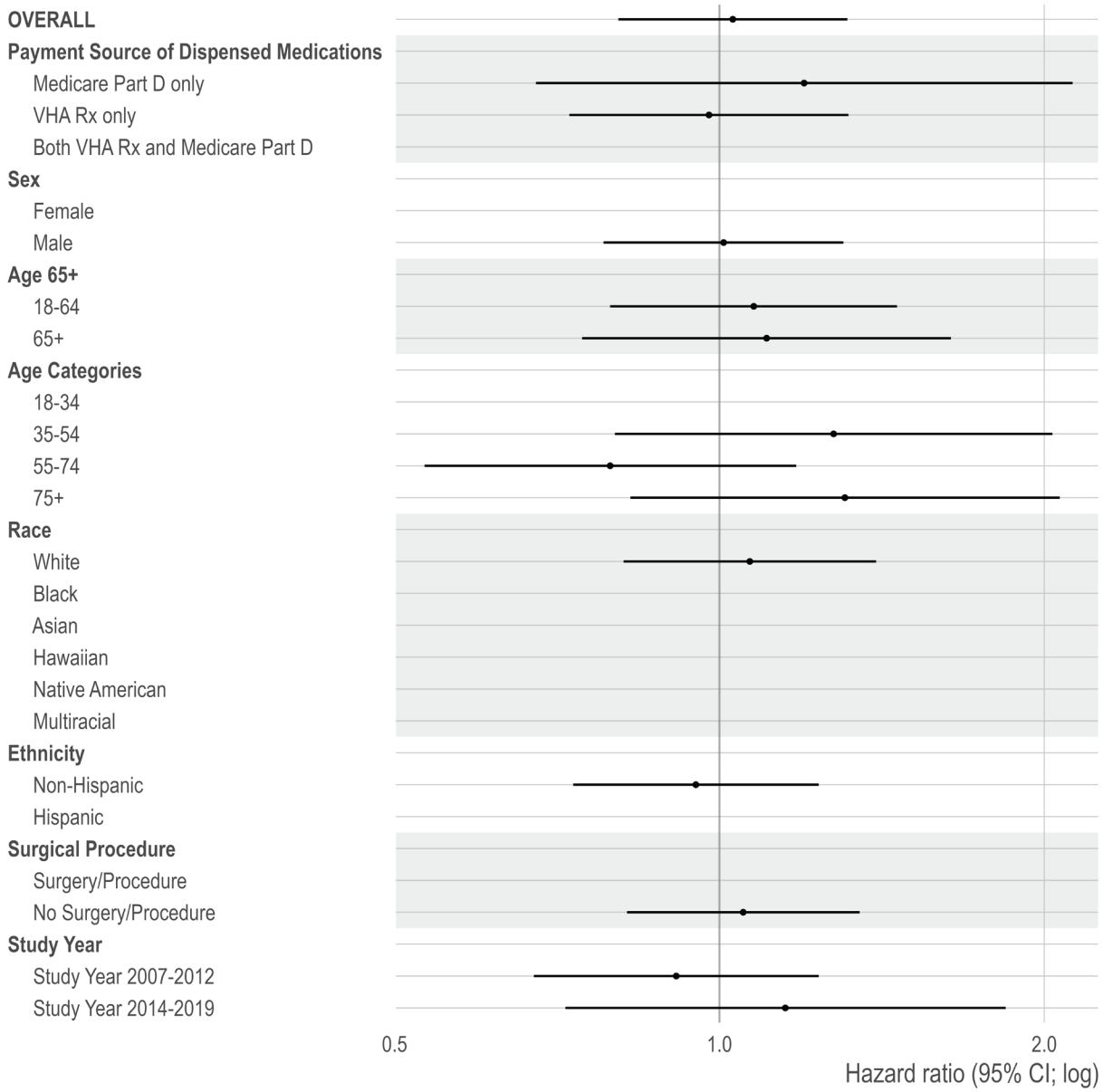

FIGURE 4-14 Study 1b. Among those with a current dispensed benzodiazepine pharmacotherapy, adjusted hazard ratios of suicide mortality between veterans with newly dispensed opioid pharmacotherapy versus veterans with newly dispensed non-opioid pain pharmacotherapy by subgroups (2007–2019; $N = 319{,}990$) (forest plots).
NOTE: No cells are reported representing 10 or fewer veterans.

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5

The Effect of Opioid Escalation on All-Cause Mortality, Including Suicide Mortality

INTRODUCTION

Within a group of those newly dispensed opioid pharmacotherapy, specific prescribing practices and patterns may result in varying levels of risk for death (Coyle et al., 2018). Of particular concern to individuals, clinicians, and policy makers is whether opioid dosage changes have an impact on the potential for harm. In this chapter, the committee focuses on the effect of opioid dosage escalation on all-cause mortality and suicide mortality. Appendix E describes the committee's assessment of studies examining the effect of dosage reductions on mortality.

Two primary causes of death, overdose and suicide, have been discussed as the predominant means by which opioid dosages may influence mortality, although other mechanisms are possible (Bohnert and Ilgen, 2019; Oquendo and Volkov, 2018; Racine, 2018; Dunn et al., 2010). The daily dosage and duration (i.e., cumulative dosages) of prescribed opioid pharmacotherapy along with concurrent prescriptions of sedating pharmacotherapy (e.g., benzodiazepines, gabapentinoids) may influence respiratory depression, contributing to fatal and nonfatal overdoses (Hahn et al., 2022; Dasgupta et al., 2016; Ilgen et al., 2016; Park et al., 2015; Bohnert et al., 2011b). Prescribing an individual a large dosage of opioid pharmacotherapy may also provide lethal means for suicide among those at risk (Magarbeh et al., 2023; Gomes et al., 2011; Sarchiapone et al., 2011), and chronic pain is a risk factor for suicide mortality (Racine, 2018; Ilgen et al., 2010). Additional possible mechanisms of death associated with higher opioid dosages include infections (Chung et al., 2021), falls (Santosa et al., 2020), motor vehicle crashes (Chihuri and Li, 2019; Li and Chihuri, 2019), wound and violence-related injuries (Hayes et al., 2020), incident cardiovascular disease (Sung et al., 2024), and psychological factors, such as new-onset depression (Salas et al., 2017).

Opioid tolerance is the pattern of deriving less analgesic effect after sustained and continuous use of opioid pharmacotherapy (Cahill et al., 2016). Given that tolerance is a common result of consistent use of opioid pharmacotherapy, opioid dosages may increase over time to achieve the same degree of analgesia, and may differ between individuals (Mercadante et al., 2019). Tolerance can be observed in as little as a few days or weeks of repeated use (Morgan and Christie, 2011). This tolerance does not apply to effects such as respiratory suppression, which is dose dependent (Hayhurst and Durieux, 2016). As a result, guidance for prescribing opioids is to "start low and go slow" until pain control is achieved (Forbes, 2011). Additionally, the U.S. Department of Veteran Affairs (VA)/Department of Defense (DoD) and Centers for Disease Control and Prevention (CDC) Clinical Practice Guidelines for Prescribing Opioids and other sources caution against increasing doses to higher levels (Sandbrink et al., 2023, 2020; VA/DoD, 2022, 2017; Dowell et al., 2022, 2020, 2016). However, the threshold of what constitutes a "low"

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versus "high" opioid dose is inconsistent in the literature and initial opioid doses vary. Additionally, there may be variation in how different individuals respond to the same opioid dose.

Prior studies indicate that higher opioid doses over longer durations are generally associated with greater overdose risk, although contextual factors, such as whether the individual was opioid naïve, are also important (Binswanger et al., 2022; Weiner et al., 2022; Bohnert et al., 2011a). The pacing of dosage changes also appears to have an influence on the risk of overdose (FDA, 2022). Thus, both the initial opioid dosage and pace of dosage increases are aspects of opioid prescribing for which different clinicians have reasonably varied in their practices.

A number of studies have found an association of higher versus lower dosages with risk of overdose, suicide, and all-cause mortality. However, these studies have not had "new user" designs that strengthen the potential for causal inference. Among individuals receiving care at the Veterans Health Administration (VHA) system specifically, higher compared to lower opioid dosages have been found to be associated with an increased risk of overdose in a dose–response fashion (Bohnert et al., 2011a). For example, relative to a dosage of 1 to < 20 morphine milligram equivalents (MMEs) per day, 20 to <50, 50 to <100, or ≥100 MMEs was associated with 1.90, 4.60, and 7.20 times the risk of fatal overdose, respectively, among individuals with a chronic pain diagnosis. This finding held across subgroups of individuals defined by having a cancer diagnosis, an acute pain episode, or a substance use disorder (SUD). The effect estimates observed in the subgroups differed from the overall sample, pointing to the importance of assessing heterogeneity of effects. Furthermore, this association was also present in a VHA study with the outcome of fatal suicide, with no difference in effect size estimates for intentional overdoses versus other forms of suicide but lower effect sizes than for unintentional overdose (Ilgen et al., 2016). Additionally, studies in a number of non-VHA samples or studies focused on overdose mortality or all-cause mortality have resulted in similar inferences (Binswanger et al., 2022; Baumblatt et al., 2014; Dunn et al. 2010).

In addition to high achieved daily opioid dosages, rates of dosage escalation may contribute to mortality. However, only a limited number of studies have examined the effects of dosage escalation on mortality (Binswanger et al., 2022; Hser et al., 2020; Dunn et al., 2010) or other outcomes in the U.S. general population or within the VHA setting (Hayes et al., 2020; Salas et al., 2017; Henry et al., 2015). Studies of opioid dosage escalation in the VHA focused on outcomes other than mortality, including new-onset depression (Salas et al., 2017), SUDs, and non-mortality opioid-related adverse outcomes (Hayes et al., 2020). Salas and colleagues (2017) found that faster rates of dosage escalation contributed to new-onset depression independent of maximum dosage, pain scores, and total duration of opioid pharmacotherapy among veterans with new long-term opioid use who did not have depression at baseline. Among veterans with chronic non-cancer pain, Hayes and colleagues (2020) reported that escalating opioid dosages were associated with increased risks of subsequent SUDs and opioid-related adverse outcomes, including accidents resulting in wounds/injuries, alcohol- and medication-related accidents and overdoses, and self-inflicted injuries. Additionally, a non-VHA study using data from the California prescription drug monitoring program found that both faster opioid dosage escalations and higher eventual dosages contributed to heightened risk of all-cause mortality (Hser et al., 2019). A study conducted in three health systems in Colorado and Wisconsin identified five opioid dosing trajectories over a 1-year period: decreasing (tapering or discontinuation), high-dose increasing (dose escalation), and three stable trajectories (dosage maintenance). Compared with the stable dosing, dosage escalation was associated with increased risk of mortality (Binswanger et al., 2022).

Some conventional studies using electronic health records (EHRs) or claims data are designed in ways that immortal time bias is present: they lack a systematic definition of "time zero," that is, a calendar date that is specific to an individual and akin to the date of randomization in a clinical trial. Having a systematically defined "time zero" in a study ensures that the beginning of follow-up time (the period for which the study team observes outcomes) and treatment initiation are synchronized. This is important because misalignment between follow-up time and treatment strategy assignment, sometimes referred to as "time-anchor misalignment," can strongly bias the results of studies in a number of ways (Hernán et al., 2016). This is especially true when the outcome is all-cause or cause-specific mortality, although misalignment can bias studies with nonfatal outcomes as well (Liang et al., 2016).

In the context of studies of dosage increases, the focus of this chapter, clear potential biases can result from comparing individuals who have been prescribed opioid pharmacotherapy for different lengths of time and with varying treatment histories. Most notably, individuals who have tolerated high daily dosages for a long time are

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likely different from those with limited opioid exposure in ways that are difficult to capture through medical records, especially in their propensity to have side effects and adverse reactions. For example, there may be "survival effects" when those likely to experience harms from opioid pharmacotherapy do so early within a course of treatment. This can introduce bias in the direction of underestimating the risk of high dosages because individuals will have been less likely to have had serious adverse effects if they progressed to higher daily dosages. Alternatively, if longer treatment durations increase risk of death independently from dosage, results will be biased to finding a harmful effect of dosage if time since starting treatment is not accounted for in the study design.

The committee noted that prior studies of opioid dosage on mortality both in and outside of the VHA have not used the target trial emulation (TTE) framework and are likely to have significant time-anchor misalignment (Hernán and Robins, 2016). As a result, a critical gap remains in understanding the relationship between opioid dosage increases and mortality among veterans. Given this gap, the committee determined that conducting a study using a causal inference–focused design on the effect of opioid dosage increases was an essential component of the statement of task to focus on "the effect of higher doses relative to lower doses of opioids."

The objective of study 2 is to identify the causal effect of varying initial opioid dosage and varying dosage escalation strategies on the risk of all-cause mortality and suicide mortality among veterans receiving care at the VHA. To address the gaps in studies that have limited ability to infer causality, the committee used a TTE framework to emulate two randomized trials. In one emulated trial,[1] individuals would be randomized to new dispensing of opioid pharmacotherapy at different baseline dosages. In the other, individuals would be randomized to different dosage escalation strategies. Treatments in each emulated trial occurred over the next 6 months. The primary outcome is all-cause mortality, and the secondary outcome is suicide mortality.

STUDY 2 METHODS

Study 2 aimed to answer the following research question: among veterans receiving care in the VHA who were newly dispensed[2] full-agonist[3] opioid pharmacotherapy between 2007–2019, what is the effect of different initial opioid dosage and escalation strategies on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) within a 12-month follow-up period?

The committee designed this study, which is an analysis of observational data to emulate two target trials. Both examine all-cause mortality and suicide mortality as outcomes; study 2a examines initial opioid dosage, and study 2b examines dosage escalation. The target trial is the hypothetical randomized pragmatic trial that would have best answered the causal question. TTE framework has two steps: (1) specify the protocol of the target trial, and (2) specify how the target trial will be emulated using observational data. The TTE framework is useful because, when applied correctly, it helps to ensure comparison of realistic treatment strategies, avoids biases from misalignment of time anchors (time zero/index date), and uses enhanced statistical techniques for minimizing confounding (Gomes et al., 2022; Hernán and Robins, 2016).

The protocol and specifications of the target trial and how the committee emulated the target trial using observational data are described in the following subsection and summarized in Table 5-1. In addition, given the complexity of each study, the committee developed Figure 5-1, which reflects key temporal aspects of the longitudinal study design, specifically the index or date of entry into the study, exposure washout period, windows for exclusion and covariate assessments, and follow-up time (Schneeweiss et al., 2019).

[1] In this report, the committee uses the terms "emulated target trial" and "study" synonymously when referring to the committee's studies and corresponding analyses.

[2] The committee notes differences in types of pharmacy data measures. Pharmacy data can be categorized into three measures: *prescribed* (prescriber submits a prescription to a pharmacy), *filled* (pharmacy completes the requested prescription), and *dispensed* (individual picks up/is mailed the prescription from the pharmacy). The committee used dispensed pharmacy data in its analyses.

[3] There are two types of opioids: full agonist and partial opioid agonist. Full opioid agonists fully activate the mu receptors in the brain, enabling the opioid to have "full" effect, such as morphine, codeine, oxycodone, and fentanyl. Partial opioid agonists also activate mu receptors in the brain but to a lesser degree, such as butorphanol or tapentadol.

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TABLE 5-1 Specifications for Study 2 Target Trial Protocol

Protocol Component	Target Trial	Target Trial Emulation
Eligibility Criteria	• U.S. veteran • Age ≥18 years • At least one encounter in Veterans Health Administration (VHA) during 2007–2019 • Valid Social Security number • No qualifying dispensed full-agonist opioid pharmacotherapy in the 90-day pre-index period • No >90-day dispensed supply of opioid pharmacotherapy in the last 12 months • First eligible dispensed opioid pharmacotherapy before January 1, 2019 • No hospice or palliative care within past 12 months • No cancer diagnosis within past 12 months (except non-melanoma skin cancers) • No dispensed medications for opioid use disorder (MOUD) formulation of buprenorphine, methadone, or levo-alpha acetyl methadol (LAAM) in 90-day pre-index period • No inpatient surgery (past 3 months) • No inpatient or outpatient procedure (past 3 months) • No acute painful injury (past 3 months) • No index month average daily morphine milligram equivalent (MME) above 50 MME/day • No encounter or dispensed pharmacotherapy in Guam, Manila, Singapore Department of Veterans Affairs (VA) facilities Baseline is defined at the first month in which all eligibility criteria are met. There were two separate trials: • Trial 2a: initial baseline dosage low, medium, or high baseline opioid dosage. • Trial 2b: escalation opioid dosage: stable, slow, or fast dosage escalation strategies.	Same as target trial
Treatment Strategies	**Trial 2a: (Initial Dosage Strategies (i.e., average dose in the first month after Day 0)):** Each eligible individual is randomly assigned to one of three initial dosage strategies: • Low (>0 to ≤20 MME) • Medium (>20 to ≤40 MME) • High (>40 to ≤50 MME[1]) **Trial 2b[2]: (Dosage Escalation Strategies, change per month in the treatment period)** Each eligible individual is randomly assigned to one of three dosage escalation strategies: • Stable (0 to <5 MME) • Slow (≥5 to <10 MME) • Fast (≥10 to ≤20 MME)	Same as target trial Defined the date of pharmacotherapy initiation to be the first calendar month of a dispensed pharmacotherapy.
Treatment Assignment	Individuals are randomly assigned to a strategy at baseline and are aware of their assigned strategy.	Assumed randomized conditional on baseline covariates (sociodemographics, health conditions and behaviors, supplemental health insurance to VHA coverage, health care utilization, specific pharmacotherapies, facility, facility-level characteristic, and calendar month of eligible dispensed pharmacotherapy)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 5-1 Continued

Protocol Component	Target Trial	Target Trial Emulation
Outcomes	Primary: All-cause mortality Secondary: Suicide mortality	Same as target trial
Start and End of Follow-Up	For each individual, follow-up starts at strategy assignment or treatment initiation (baseline). Eligible individuals are followed from time until death (or death to other causes, in analysis of suicide mortality), cancer diagnosis (except non-melanoma skin cancer), receipt of hospice or palliative care during follow-up, and/or receipt of MOUD or naltrexone during follow-up, censoring by discontinuation or administrative end of follow-up at 12 months, whichever occurs first.	Same as target trial
Causal Contrast	Per protocol effect The primary effect is the total effect of the specified intervention strategies on mortality through all causal pathways between the interventions and the outcome. For the secondary outcome of suicide, the primary effect includes causal pathways potentially mediated by death from other causes (a competing event).	Observational analogue of per protocol effect
Statistical Analysis	Per protocol analysis. Parametric G-formula to compare risk under each treatment strategy (increasing baseline dosage; increasing escalation dosage) via mortality risk and risk ratio. Only eligible months with sustained treatment were included in the model building stage.	Same as target trial

[1] The committee determined a threshold of 50 Morphine Milligram Equivalents per Day (MMED) as the intent of the study was to look at opioid naïve individuals. Based on their clinical expertise, the committee determined that individuals prescribed a dose greater than 50 MMED would likely not be opioid naïve.

[2] The committee arrived at these thresholds based on discussion with clinicians regarding usual trajectories in clinical practice, as well as clinical appropriateness of dosage strategies.

SOURCE: Adapted from Hernán and Robins, 2016, and NASEM, 2019.

Study Population and Data Sources

The study population was defined as veterans receiving care in the VHA, and the study period was from January 1, 2007, to December 31, 2019.[4] The earliest index date, or start date, was January 1, 2007.[5] The latest possible index date was December 31, 2018, to allow individuals to be followed for 12 months after being newly dispensed opioid pharmacotherapy. To assess exclusion and eligibility in the study and follow-up, data from 2006–2019 were pulled for analyses.

Data from the national VHA data files were linked to the VA Corporate Data Warehouse, U.S. Veterans Eligibility Trends and Statistics, National Death Index (NDI), and Medicare Parts A, B, C, and D data from the Centers for Medicare & Medicaid Services (CMS). Primary sources for individual inclusion/exclusion criteria and covariates were from VA and VHA data. CMS data were used to supplement individual data used for inclusion/exclusion and other covariates. Data files were linked based on a veteran's unique individual integrated control number, Social Security number (SSN), and date of birth. The National Academies of Sciences, Engineering, and Medicine Institutional Review Board approved the study.

[4] Latest possible index date was December 31, 2018, in study 2.

[5] Given that the earliest index date is January 1, 2007, the earliest pre-index data are January 1, 2006.

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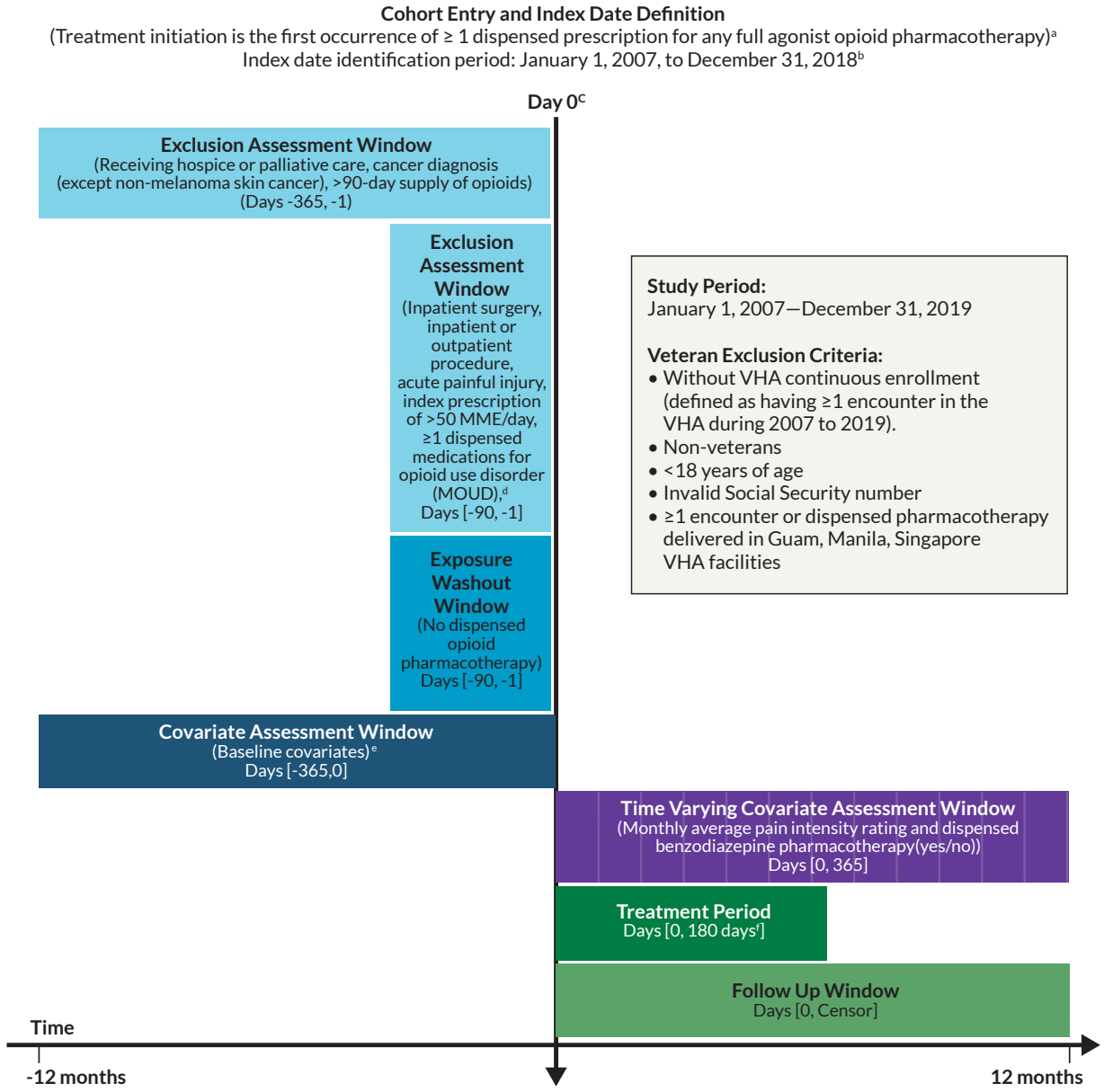

Notes:
a. Treatment initiation: ≥1 newly dispensed prescription for any full agonist opioid pharmacotherapy (including tramadol) without any dispensed opioid pharmacotherapy in the preceding 90 days.
b. Index and follow-up: Every individual with an eligible dispensed prescription during the index date period is followed through to December 31, 2019, for all episodes. First eligible episodes starting after January 1, 2019 are not included.
c. Day 0 is individual dependent and is not anchored to a specific date.
d. MOUD: Formulations of buprenorphine, methadone, LAAM, or naltrexone from prescription data and clinic stop codes.
e. The most recent values for age, sex, race, and ethnicity in individual electronic health records were used.
f. Misalignment between follow-up time and treatment initiation, sometimes referred to as "time anchor misalignment," can strongly bias the results of studies in a number of ways. However, Parametric G-formula methods overcome this problem through the use of a simulation.

FIGURE 5-1 Study 2 design.
NOTE: No cell sizes of 10 or less are included in the reported result.

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SPECIFICATIONS FOR THE EMULATED TARGET TRIAL 2

Drawing from this study population of all veterans who received care in VHA facilities, this study focused on those who were dispensed ≥1 any full agonist opioid (including tramadol) in the outpatient setting. Figure 5-2 illustrates the flowchart detailing the selection process of including eligible veterans in study 2. The following section outlines each of the TTE components for study 2.

Study 2 Eligibility Criteria

For each calendar month from January 1, 2007, to December 31, 2019, the committee identified eligible individuals who met the following criteria: (1) be a U.S. veteran; (2) be 18 years or older; (3) have a valid SSN; and (4) have at least 1-year continuous enrollment in the VHA between 2006–2019,[6] defined as at least one encounter in the VHA in the 12-month pre-index period. Eligible individuals also included veterans with at least one encounter in the VHA in the 12 months before the index date within the eligible study period but only had a pharmacy claim through Medicare Part D (no VHA pharmacy claim). In addition, those who were eligible did not have an encounter or dispensed pharmacotherapy in Guam, Manila, Singapore VHA facilities. These veterans were excluded given that mortality data collected in these regions are not reflected in the NDI data. See "exclusion criteria" for further information.

To be eligible for study 2, VHA veterans had to have no dispensed opioid pharmacotherapy in the 90-day pre-index period (the exposure washout period). The committee established this washout period, based on the following considerations in addition to committee expertise (VHA, 2006):

1. Maximum duration of any opioid prescription for non-hospice/non-palliative care is 90 days.
2. The maximum duration of any prescription fill in the VA is 90 days, with exceptions for Schedule 2 drugs such as oxycodone prescriptions, which have a maximum duration of 30 days (except for individuals in hospice or palliative care).[7]

In addition, VHA veterans meeting the eligibility criteria must not have been dispensed[8] full-agonist opioid analgesics, including tramadol, in the 90-day pre-index period (the exposure washout period) and 365 days preceding their index fill (i.e., dispensed full-agonist opioid pharmacotherapy) to ensure that eligible participants were newly dispensed opioid pharmacotherapy on the index date. Requiring a washout period facilitated the committee's ability to examine the effects of opioid dosage increases among individuals newly dispensed an opioid pharmacotherapy and avoid the issues described that result from comparing across individuals with different treatment histories.

Study 2 Eligibility Exclusion

Study 2 had an exclusion assessment window of 365 days before the index date. VHA veterans who received hospice or palliative care or had a cancer diagnosis (except non-melanoma skin cancers) were excluded from the study. International Classification of Disease (ICD) diagnosis codes were used to identify conditions (see Appendix I for list of codes). Individuals receiving palliative care and/or in hospice were excluded given that having a terminal illness (and thus eligible for these services) is related to both death and more permissive use of opioid pharmacotherapy and thus is a confounder in the relationship between receiving opioid pharmacotherapy and death. In addition, individuals with cancer have an increased risk of mortality and often receive an opioid pharmacotherapy

[6] Given that the earliest index date is January 1, 2007, the earliest pre-index data are January 1, 2006.

[7] Hydrocodone was changed from a Schedule III drug to a Schedule II drug on October 6, 2014; before this, there could be 90-day fills of hydrocodone, which was common in VA and elsewhere.

[8] The committee notes differences in types of pharmacy data measures. Pharmacy data can be categorized into three measures: prescribed (prescriber submits a prescription to a pharmacy), filled (pharmacy completes the requested prescription), and dispensed (individual picks up/is mailed the prescription from the pharmacy). The committee used dispensed pharmacy data in its analyses.

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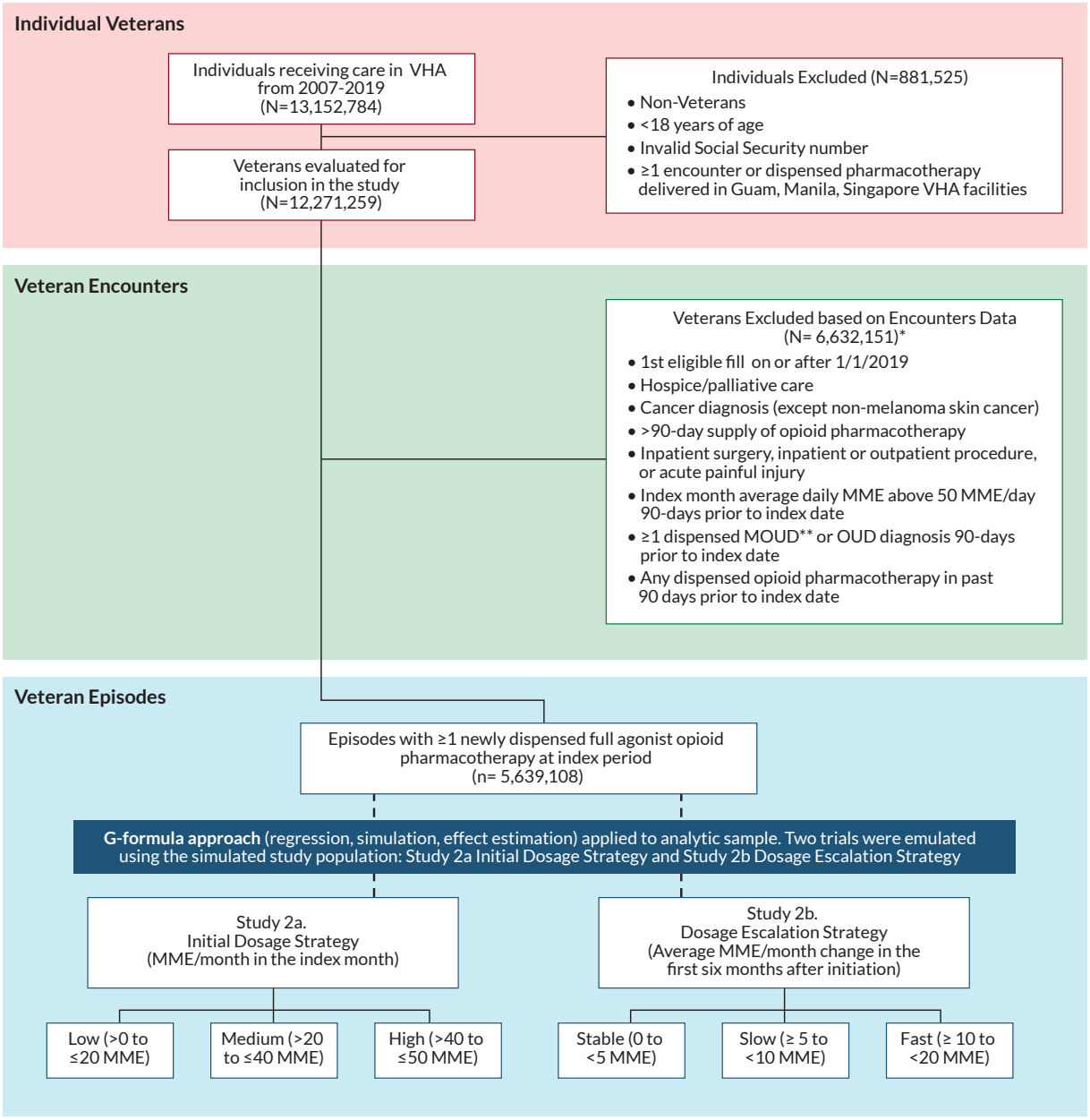

Notes:
* Exclusions made before baseline (at 12 months, unless indicated otherwise) and not based on post-baseline information. See also Figure 5-1 exclusion assessment windows for timing information.
** Dispensed MOUD formulations of buprenorphine, methadone, LAAM, or naltrexone, including claims with VA prescription stop codes.
MOUD: medication for opioid use disorder; OUD: opioid use disorder.

FIGURE 5-2 Selection of veterans through each stage of the emulated target trials (study 2a and study 2b) (2007–2019).
NOTE: No cell sizes of 10 or less are included in the reported result.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

to manage cancer-related pain. Decisions regarding opioid initiation, co-prescribing, and dosage increases may differ for cancer compared to non-cancer pain; policies and practices for opioid prescribing is (generally) more permissive for individuals with cancer (VA/DoD, 2022, 2017, 2010, and 2003; Manchikanti et al., 2017; Dowell et al., 2016; Nersesyan and Slavin, 2007). Furthermore, study exclusion criteria are in line with published studies examining opioid pharmacotherapy, which exclude individuals with cancer (Song et al., 2022; Coyle et al., 2018; Berna et al., 2015; Turner and Liang, 2015; Gomes et al., 2011; Dunn et al., 2010). As a result, having cancer may be a confounder between treatment regimen and mortality, and individuals with cancer are excluded.

The committee excluded VHA veterans receiving medications for opioid use disorder (MOUD), formulation of levo-alpha acetyl methadol (LAAM), methadone (based on clinic stop codes), buprenorphine, or naltrexone), and/or initial opioid dosages of at least 50 MME/day[9] in the 90-day pre-index period to reduce the likelihood of including those who were not truly opioid naïve. In addition, due to complexities to measuring MME exposure, the committee excluded any individuals in the population who had received ≥1 dispensed MOUD formulation of LAAM, methadone, buprenorphine, or naltrexone in the 90-day pre-index period.

Veterans with qualifying episodes[10] beginning on or after January 1, 2019, were excluded to ensure that each veteran included in the study had the potential for a complete 12-month follow-up period.

Given the study's causal question, additional exclusion criteria were applied. These criteria were designed to ensure that the study population was relevant to the causal question. The following individuals were excluded: those who had acute painful injury diagnoses, surgeries, procedures (based on current procedural terminology codes [also known as CPT codes]) in their EHRs in the 3 months prior to index date, because dosage increases are not an expected component of short-term or acute opioid prescribing.

Based on the inclusion/exclusion criteria listed, Figure 5-2 illustrates the flowchart detailing the selection process of veterans for the two emulated target trials.

Study 2 Treatment Strategies

Drawing from this study population of eligible veterans, this study considers the following clinically realistic treatment strategies. There were two studies conducted: study 2a: treatment groups were selected to represent alternative strategies for initial opioid dosage (see Table 5-2), and study 2b: escalation strategies over 6 months after initiation (i.e., from a daily dosage of 0) (study 2b) (see Table 5-3).

- For study 2a, the committee considered three initial dosage levels based on its clinical expertise and review of the observed distribution in the data: 1) >0 to ≤20 MME/day (low), 2) >20 to ≤40 MME/day (medium), and 3) >40 to ≤50 MME/day (high).
- The committee considered the following scenarios of opioid dosage escalation for study 2b: 1) stable dosage, an average of 0 to <5 MME/day increase per month for 6 consecutive months (stable), 2) an average of ≥5 to <10 MME/day increase per month for 6 consecutive months (slow), and 3) an average of ≥10 to <20 MME/day increase per month for 6 consecutive months (fast). The average MMEs to assign individuals to specific trajectories were calculated using a rolling average, adjusted to a 30-day average. See also Tables 5-2 and 5-3 for the categories.

The list of eligible opioid and non-opioid pain pharmacotherapies is in Table 5-4.

Study 2 Treatment Assignment

In the hypothetical target trial, eligible individuals would be randomly assigned by clinical researchers to a treatment strategy with their consent and followed; individuals would be aware of their treatment assignment. In the emulated target trial (study 2), based in retrospective observational data, treatment assignments were based on the observed dispensed prescription drug events (claims) from Medicare Part D or dispensed pharmacotherapies from the VHA EHRs. Thus, the analyses considered prescription dispensing records to assign treatment strategy,

[9] Initial dosages higher than 50 MME/day or greater were unusual (7.21 percent of analytical sample).
[10] All veteran episodes (regardless of treatment assignment).

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TABLE 5-2 Study 2a: Initial Dosage Strategies

Initial opioid dosage strategy (MME[1]/Day)
Low (>0 to ≤20)
Medium (>20 to ≤40)
High (>40 to ≤50)

[1] MME: Morphine milligram equivalent.

TABLE 5-3 Study 2b: Dosage Escalation Trajectories

Dosage opioid escalation strategy (Average MME[1]/Day change in 6 months)
Stable (0 to <5)
Slow (≥5 to 10)
Fast (≥10 to <20)

[1] MME: Morphine milligram equivalent.

unlike in the hypothetical target trial, for which researchers would determine the treatment assignment, which could be different from what medications[11] ultimately were dispensed. It is also important to distinguish the measurability of prescription dispensing data from the measurability of that which is ingested by the individual. A dispensed prescription does not necessarily mean that the medication was consumed, since these medications are commonly prescribed to be taken "as needed." For this study, a measure of individuals ingesting the prescription was not available in the dataset analyzed; the committee used prescription dispensing data as a proxy for medications ingested by the individual. After the first dispensed eligible pharmacotherapy, 30-day pharmacotherapy episode interval was created for eligible veterans.

Selection of Pharmacotherapies of Interest and Measures in Study 2. Using a combination of VA and Medicare Part D data, the committee identified full opioid agonists for pain management, excluding MOUD (see Table 3-4 for a complete list of eligible medications). To specify the newly dispensed opioid pharmacotherapy, individuals with only full agonists (including tramadol) were considered eligible for the opioid-exposed group; however, once in that group, individuals could additionally be dispensed atypical opioid pharmacotherapy (tapentadol or butorphanol). The MMEs from these pharmacotherapies were included in the total dosage calculations of the group.

Measuring Opioid Dosage. The intensity of opioid use was measured based on MMEs, which is ideal because it standardizes dispensed opioid pharmacotherapy considering differences in the potency, quantity, and strength of different types of opioid pharmacotherapy. The committee excluded injectable opioid pharmacotherapy because they have different MME conversion factors from oral opioid pharmacotherapy and are uncommon in outpatient settings. The committee calculated MMEs using conversions from the CDC (Dowell et al., 2022). The committee measured the mean daily MME dosage per 30-day period using an "on-therapy days," as defined in Dasgupta and colleagues (2021), which accounts for overlapping opioid prescriptions with no gap allowances made for early refills. The numerator is the sum of MMEs across all prescriptions dispensed in discrete 30-day periods of time from the index date. The denominator is the total number of unique days with opioid exposure based on days' supply, counting overlap days once. Dispensed opioid pharmacotherapy data with missing variables (e.g., days' supply, National Drug Code) required to calculate MMEs were excluded (Dasgupta et al., 2016).

[11] The committee uses the term "pharmacotherapy" throughout the report instead of "medications," "prescriptions," or "treatment," especially when referencing the committee's analyses and results.

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Table 5-4 Pharmacotherapies of Interest in Study 2

Drug Class	Study 2
Opioid Full Agonist	
Benzhydrocodone	Opioid pharmacotherapy (Treatment)
Codeine	Opioid pharmacotherapy (Treatment)
Dihydrocodeine	Opioid pharmacotherapy (Treatment)
Fentanyl	Opioid pharmacotherapy (Treatment)
Hydrocodone	Opioid pharmacotherapy (Treatment)
Hydromorphone	Opioid pharmacotherapy (Treatment)
LAAM[1] (non-liquid; for pain)	Opioid pharmacotherapy (Treatment)
LAAM (non-liquid; MOUD[2])	• Included in baseline exclusion criteria • Censored during follow-up
Levomethadyl	Opioid pharmacotherapy (Treatment)
Levorphanol	Opioid pharmacotherapy (Treatment)
Meperidine (oral)	Opioid pharmacotherapy (Treatment)
Methadone (non-liquid/non-diskette) (for pain)	Opioid pharmacotherapy (Treatment)
Methadone (non-liquid/non-diskette) (MOUD)	• Included in baseline exclusion criteria • Censored during follow-up
Morphine	Opioid pharmacotherapy (Treatment)
Oxycodone	Opioid pharmacotherapy (Treatment)
Oxymorphone	Opioid pharmacotherapy (Treatment)
Propoxyphene	Opioid pharmacotherapy (Treatment)
Sufentanil (sublingual)	Opioid pharmacotherapy (Treatment)
Tramadol	Opioid pharmacotherapy (Treatment)
Opioid Atypical	
Buprenorphine (MOUD)	• Included in baseline exclusion criteria • Censored during follow-up
Buprenorphine (for pain)	• Included in baseline exclusion criteria • Not censored during follow-up • Incorporated into morphine milligram equivalent (MME) calculations during follow-up
Butorphanol	• Included in baseline exclusion criteria • Not censored during follow-up • Incorporated into MME calculations
Tapentadol	• Included in baseline exclusion criteria • Not censored during follow-up • Incorporated into MME calculations
Opioid Antagonist	
Naltrexone	• Included in baseline exclusion criteria • Censored during follow-up

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 5-4 Continued

Drug Class	Study 2
Benzodiazepine	
Alprazolam	Confounder
Bromazepam	Confounder
Chlordiazepoxide	Confounder
Clobazam	Confounder
Clonazepam	Confounder
Clorazepate	Confounder
Diazepam	Confounder
Estazolam	Confounder
Flurazepam	Confounder
Halazepam	Confounder
Lorazepam	Confounder
Oxazepam	Confounder
Prazepam	Confounder
Quazepam	Confounder
Remimazolam	Confounder
Temazepam	Confounder
Triazolam	Confounder
Anti-Convulsant	
Carbamazepine	Confounder
Oxcarbazepine	Confounder
Topiramate	Confounder
Antidepressants	
Amitriptyline	Confounder
Amoxapine	Confounder
Bupropion (Tab)	Not included in study
Citalopram	Not included in study
Clomipramine	Confounder
Desipramine	Confounder
Desvenlafaxine	Confounder
Doxepin	Confounder
Duloxetine	Confounder
Escitalopram	Not included in study
Esketamine	Not included in study
Fluoxetine	Not included in study
Fluvoxamine	Not included in study
Impramine	Confounder
Isocarboxazid	Not included in study

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 5-4 Continued

Drug Class	Study 2
Levomilnacipran	Confounder
Milnacipran	Confounder
Mirtazapine	Confounder
Nefazodone	Not included in study
Nortriptyline	Confounder
Paroxetine	Not included in study
Phenelzine	Not included in study
Protriptyline	Confounder
Selegiline	Not included in study
Sertraline	Not included in study
Tranylcypromine	Not included in study
Trazodone	Not included in study
Trimipramine	Confounder
Venlafaxine	Confounder
Vilazodone	Not included in study
Viloxazine	Not included in study
Vortioxetine	Not included in study
Antihistamine	
Hydroxyzine	Confounder
Anxiolytic	
Buspirone	Confounder
Gabapentinoids	
Gabapentin	Confounder
Pregabalin	Confounder
Insomnia	
Eszopiclone	Not included in study
Ramelteon	Not included in study
Suvorexant	Not included in study
Zaleplon	Not included in study
Zolpidem	Not included in study
Migraine	
Almotriptan	Confounder
Aspirin w/ caffeine	Confounder
Eletriptan	Confounder
Fioricet	Confounder
Fioridals	Confounder
Fioridan	Confounder
Frovatriptan	Confounder
Naratriptan	Confounder

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 5-4 Continued

Drug Class	Study 2
Rizatriptan	Confounder
Sumatriptan	Confounder
Sumatriptan + Naproxen	Confounder
ZOLMitriptan	Confounder
Muscle Relaxers	
Baclofen	Confounder
Carisoprodol	Confounder
Chlorzoxazone	Confounder
Cyclobenzaprine	Confounder
Dantrolene	Confounder
Metaxalone	Confounder
Methocarbamol	Confounder
Orphenadrine	Confounder
Tizanidine	Confounder
Other Non-Opioid Analgesic	
Acetaminophen	Confounder
Non-Steroidal Anti-Inflammatory Drugs	
Aspirin (>=400mg)	Confounder
Celecoxib	Confounder
Diclofenac (pill)	Confounder
Diflunisal	Confounder
Etodolac	Confounder
Fenoprofen	Confounder
Flurbiprofen	Confounder
Ibuprofen	Confounder
Indomethacin	Confounder
Ketoprofem	Confounder
Ketorolac	Confounder
Meclofenamate	Confounder
Meloxicam	Confounder
Nabumetone	Confounder
Naproxen	Confounder
Oxaprozin	Confounder
Phenylbutazone	Confounder
Piroxicam	Confounder
Salsalate	Confounder
Sulindac	Confounder
Tolmetin	Confounder

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 5-4 Continued

Drug Class	Study 2
Serotonin-Norepinephrine Reuptake Inhibitor	
Desvenlafaxine	Confounder[3]
Venlafaxine	Confounder[3]
Tetracyclic Antidepressant	
Mirtazapine	Confounder[3]

[1] LAAM: Levo-Alpha Acetyl Methadol.
[2] MOUD: Medication for opioid use disorder.
[3] Desvenlafaxine, venlafaxine, and mirtazapine are included in study 2 in the antidepressant covariate.

Study 2 Start and End of Follow-Up

The start date, or index date, is when the eligible veteran was first dispensed the qualifying ≥ 1 full-agonist opioid medication and when all baseline eligibility criteria were met. To facilitate computation, the index date was transformed into an index month, and all analyses were conducted using aggregated monthly data. Based on the study design that considered a 12-month pre-index period and a 12-month follow-up period, January 1, 2007, was the first eligible index date and December 31, 2018, was the last eligible index date. The committee utilized all available follow-up data (through the end of 2020) with prespecified landmark analysis at 12 months.

To estimate the effect of opioid dosage escalation on mortality, the analysis limited follow-up to 12 months. The study timeline start is based on the calendar month in which the individual was dispensed the index prescription.[12]

For the per protocol analysis, given that interest is in observing the effect of initiating and continuing the treatment strategy over a specified follow-up period, eligible individuals are followed from treatment initiation (baseline) until death (or death due to other causes in analysis of suicide mortality), cancer diagnosis (except non-melanoma skin cancer), receipt of hospice or palliative care, or the administrative end of follow-up (at the end of 12 months from baseline), whichever happens first.

Outcomes

The outcomes outlined in the statement of task are all-cause mortality and suicide mortality, which were identified through linked data from NDI. The committee determined all-cause mortality as the primary outcome and suicide mortality as the secondary outcome. Suicide mortality is identified by the ICD-10 death codes X60-X84 (intentional self-harm), U03 (intentional self-harm (suicide)), and Y87.0 (sequelae of intentional self-harm) (Hirsch et al., 2016; CDC, 2002).

Causal Contrast: Per Protocol Effect

The causal contrast for study 2 was the per protocol effect. The parametric G-formula was used to estimate the per protocol effect. This approach is useful for studying interventions that are defined as a course of a stable treatment for a certain length of time or one that changes under specific conditions (i.e., a dynamic treatment strategy). A common issue with studying sustained treatment strategies is the problem of misalignment of time anchors. Parametric G-formula methods overcome this via simulation. The general assumptions of this approach are the same as other trial emulations–if there are no unmeasured confounders, no measurement error, and no

[12] For example, a dispensed index prescription on July 11, 2017, means that July 2017 is month 1 for the participant. MME/month are adjusted; for example the MME/month for an individual dispensed an opioid prescription would be an average over 21 days, or from July 11 to 31).

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model misspecification, the per protocol effect provides unbiased estimates of causal effects. See chapter 3 for a detailed description of all the assumptions associated with this approach.

Study 2 Study Design

This study design was an active comparator new user (Lund et al., 2015; Ray, 2003), retrospective cohort TTE (Hernán and Robins, 2016). For this study, the committee sought to emulate a pragmatic clinical trial in which individuals are randomized to one of three initial baseline opioid dosages (study 2a) or one of several dosing strategies over a 6-month treatment period (study 2b).

Study 2 Covariates

To strengthen causal inferences, the committee controlled for many covariates to adjust for baseline and/or time-varying confounding and achieve balance between the treatment and comparator groups:

- Sociodemographics,
- Health conditions and behaviors,
- Supplemental health insurance to VHA coverage,
- Health care utilization,
- Specific pharmacotherapies,
- Facility-level characteristics,
- Facility, and
- Calendar month of eligible dispensed pharmacotherapy.

Additional covariates include month and the interaction between state and year as fixed effects. Baseline covariates included demographic characteristics (e.g., age, sex, race/ethnicity, marital status, disability status), supplemental insurance to VHA coverage (i.e., Medicare, TRICARE, or private insurance), housing security (e.g., history of homelessness status), physical and mental health conditions (e.g., acute painful injury, anxiety, chronic obstructive pulmonary disease, cardiovascular disease, SUDs, diabetes), military status (e.g., service era, military branch, combat service), body mass index, health care utilization in prior year (e.g., VHA outpatient visits, inpatient hospital admissions, nursing home stay), VHA facility-level characteristic (e.g., urbanicity), and specific pharmacotherapies that the committee considered as potential confounders (such as migraine pharmacotherapy, anxiolytic, benzodiazepines; see Table 3-4 and Table 5-4 for the detailed list). The committee evaluated candidate variables readily available in the study clinical and administrative databases (see Appendix I for a list of all health conditions and corresponding ICD codes).

The studies did not require participants to have a chronic pain diagnosis in the primary analysis. Studies have shown that individuals identified with chronic pain did not have a pain diagnosis or pain was underreported in electronic medical records compared to pain reported in a patient-based survey (Frank et al., 2019; Goulet et al., 2016)

Time-Varying Covariates

The time-varying covariate included pain intensity ratings (measured by the average of all documented pain scores within a month in the VA EHR) and receipt of any benzodiazepine prescriptions during the follow-up period. The time-varying covariate was updated monthly in the dataset. When a new measurement was unavailable, the last observation was carried forward indefinitely until a new measurement was available or the individual was censored.

Accounting for Secular Trends and Variation by Facility

Facility and calendar time (12 months) were captured as fixed effects to capture facility-specific variation (e.g., clustering of individuals within a facility, geographic variation by facility) and reflect changes over time

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(e.g., variation in behaviors [health care seeking, prescribing]) and prevalence of conditions during a year. The committee also included the interaction term (i.e., product term) between state and year to capture variation over time and by states, such as when state or facility policies related to opioid prescription were implemented (e.g., when states began to participate in the Prescription Drug Monitoring Program) or secular trends in state-level policies and intensities during the opioid epidemic.

Statistical Analyses

Parametric G-Formula

The committee applied the parametric G-formula to estimate the causal effect of specific patterns of opioid dosage escalation on all-cause mortality and suicide mortality. A key strength of the G-formula method is that it can estimate effects of sustained treatment strategies, as in the case of dosage adjustments under a "titrate until pain control is achieved" protocol. This is in contrast with "time point interventions," such as "start opioids for pain." A common issue with studying sustained treatment strategies is the problem of misalignment of time anchors, which can lead to several types of bias (Hernán et al., 2016). Specifically, because sustained treatment strategies lack a single time anchor, it is impossible to correctly align the treatment group assignment time anchor with the timing of eligibility assessment and start of follow-up. Parametric G-formula methods overcome this problem via simulation.

Compared to traditional observational study methods, the parametric G-formula also can address confounding when it is due to complex relationships over time, such as past-exposure-affected time-varying confounding, defined as when past treatment has a causal relationship with current covariates, which are related to future treatment and outcomes. In this study, an example is when prior opioid dosage influences the pain level, which influences both whether the opioid dosage is changed at the next appointment and risk of suicidality. Because the G-formula can appropriately handle time-varying confounding, it can account for the post-baseline factors related to adherence to a specific opioid dosage pattern when estimating the effect of those patterns on outcomes. An alternative option would be the "clone, censor, weight" approach, which can also incorporate time-varying confounding adjustment and be used to measure sustained treatment strategies, via the clone component. However, the committee was interested in estimating the causal effect of specific, well-defined opioid dosage trajectories to best mimic a clinical trial and aid interpretability of findings. The G-formula facilitates modeling of very specific dosage trajectories. Also, the G-formula was applied to studies 2a and 2b to ensure the same sample is included in both, which would allow direct comparison of the results between both studies and evaluate the relative importance of the two aspects of prescribed dosage. In summary, the committee selected the parametric G-formula because of its ability to address time-varying confounding and ensure time-anchor alignment with treatment strategies that accrue over time and because the committee is interested in estimating the impact of specific, sustained dosing strategies (e.g., 10 percent increase per month) rather than all dosing trajectories present in the data.

Broadly, the modeling strategy of the parametric G-formula is a three-step process: (1) generate prediction models using regression for all time-varying covariates used in the study and the outcome, both conditional on observed treatment and covariate history, (2) conduct Monte Carlo simulation to iteratively estimate the outcome at each follow-up time if all individuals in the sample received a specific treatment strategy (repeated for each treatment strategy), and (3) use bootstrapping (repeating steps 1 and 2) to generate standard errors for the risk estimates. The options for a threshold intervention and lag functions[13] for employing the G-formula to the study.

For the present study, using a survival time-based outcome assessment, the G-formula method produces estimates of the contrasts in failure risks (death) over 12 months between the comparator dosage strategies. This study evaluated two different components of opioid dosages in two separate analyses: (1) initial dispensed dosage (measured as average MME/day in the index month) and (2) dosage escalation (measured as the average MME/day change per month in the first 6 months after initiation). The initial dosage strategies were low (>0 to ≤20 MME/day, reference), medium (>20 to ≤40 MME/day), and high (>40 to ≤50 MME/day) in the index month.

[13] In the committee's analysis, the lag function refers to the following function: the G-formula uses prior months in the analysis for estimation of adherence and outcome. The committee used 1 month prior in the formula.

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The dosage escalation strategies were stable (0 to <5 MME/day, reference), slow (≥5 to <10 MME/day), and fast ≥10 to <20 MME/day), measured as a change per month and sustained for 6 consecutive months. The committee estimated prediction models for 12 intervals, 1 for each month in the year; measurements in each interval varied by time-varying covariates and individuals who were censored.

Within the simulation step of the G-formula, the veterans are "assigned" the intervention to estimate the outcome as if they had received that level of the intervention. For example, in the low initial dosage strategy of study 2a, the simulated study population is assigned an MME/day of 0–20 as their initial dispensed dosage and followed over 12 months to estimate their predicted risk of mortality overall. The risk of mortality (as a measure of absolute risk), expressed as a percent dying over 12 months, was then estimated for each initial dosage strategy and dosage escalation strategy. In addition, the risk ratio (RR) compared each treatment strategy to its reference. The committee estimated G-formula models three different treatment strategies in the initial dosage strategies study (study 2a) and also for the escalation dosage strategies study, for a total of six models for each treatment strategy. Confidence intervals (CIs) were calculated using the percentile method from 400 bootstrap samples (Davidson and MacKinnon, 2001). The committee used the following options in the G-formula approach in SAS software (Logan et al., 2022; McGrath et al., 2020): a time-varying indicator of failure (death or fatal suicide) and lagged month of data for time-varying covariates. Individuals were censored in the month of their censoring event using the censor option in the G-formula macro "call."

All analyses were conducted using SAS 9.4 and SAS Enterprise Guide. Study results do not report data if sample sizes were 10 or fewer individuals. This helps to ensure confidentiality of individuals in the study and be in line with CMS data policy and National Center for Health Statistics (NCHS) recommendations (NCHS, 2023; HHS, 2020). Furthermore, cells are marked as unreliable where sample sizes were 20 or fewer.

Descriptive Analyses

The committee reported the distributions of baseline demographic and clinical characteristics for the overall analytic sample.

Subgroup Analyses

Given the challenges in computing capacity and processing time, analyses on subgroups (e.g., by age, gender, race, and ethnicity) or sensitivity analyses were not conducted.

RESULTS

Among the 13,152,784 million unique veterans who received care in the VHA 2007–2019, 5,639,108 individuals qualified for inclusion in modeling. Of the individuals in the final analytic sample, there were 52,809 observed all-cause mortality deaths and 767 suicide mortality deaths in the 12 months following the index date. The characteristics of the final sample are presented in Table 5-5. As in VHA veterans in general, the sample was largely male (92.70 percent). The mean age of the population was 59.86 years (SD[14]: 16.32). By race, the population was White (71.46 percent), Black (16.21 percent), Asian (0.80 percent), Native American (0.49 percent), Pacific Islander (0.70 percent), of multiple races (0.80 percent), and those with a missing race category (9.54 percent). By ethnicity, individuals were non-Hispanic (88.73 percent), Hispanic (5.41 percent), and of missing ethnicity (5.86 percent).

The G-formula estimate for the natural course, which is the estimated percent of the study population that would die by 12 months based on the simulation models, was 4.37 percent (SE: 0.15) for the model for initial dosage strategy (study 2a) and 4.57 percent (SE: 0.16) for the model for escalation dosage strategy (study 2b). The observed risk in this study population was 6.26 percent. The difference between the natural course estimate that results from simulation models and the observed rate may reflect the impact of censoring and or imprecision in the model.

[14] Standard deviation

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 5-5 Among VHA Veterans Newly Dispensed Full-Agonist Opioid Pharmacotherapy, Baseline Characteristics of Individuals (2007–2019; N = 5,639,108)

Covariates	Percentage % (or mean)	Standard Deviation
Sex		
Male	92.70	
Female	7.30	
Age (Continuous)	(59.86)	(16.325)
Race		
White	71.46	
Black	16.21	
Asian	0.80	
Native American	0.49	
Pacific Islander	0.70	
Multiracial	0.80	
Missing	9.54	
Ethnicity		
Non-Hispanic	88.73	
Hispanic	5.41	
Missing	5.86	
Marital Status		
Married	53.20	
Unmarried	44.30	
Missing	2.50	
Disability Status (Based on VA[1] Enrollment Priority Group)		
Enrollment Group 1	22.83	
Enrollment Group 2	7.54	
Enrollment Group 3	11.84	
Enrollment Group 4	1.37	
Enrollment Group 5	35.53	
Enrollment Group 6	4.43	
Enrollment Group 7	3.02	
Enrollment Group 8	13.25	
Missing	0.27	
Housing Security		
History of Homelessness (yes/no)	10.80	
Health Behavior		
Tobacco Use Ever (Yes/No)	45.08	
Health Conditions		
Physical Health Conditions		
Pain Conditions		
Abdominal pain	11.58	
Back Pain	22.78	

continued

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Table 5-5 Continued

Covariates	Percentage % (or mean)	Standard Deviation
Fibromyalgia	1.47	
Fractures	6.22	
Headaches	5.54	
Limb Pain	38.96	
Musculoskeletal Pain	8.15	
Neck Pain	6.56	
Neuropathy	7.23	
Orofacial Pain	0.70	
Systemic Disorders	1.68	
Urogenital Pain	1.92	
Other	6.59	
AIDS/HIV	0.46	
Blood Loss Anemia	1.06	
Cardiovascular Disease	17.53	
Cerebrovascular Disease	4.41	
Chronic Lung Disease	13.14	
Cirrhosis	0.76	
COPD[2]	2.40	
Deficiency Anemia	4.81	
Dementia	2.33	
Diabetes	21.94	
End Stage Renal Disease	0.68	
Heart Disease	17.34	
Hepatitis	1.41	
Hemiplegia or Paraplegia	0.58	
Liver Disease	1.92	
Migraine	2.31	
Peptic Ulcer Disease	0.56	
Peripheral Vascular Disease	3.78	
Pulmonary Circulation Disorders	0.17	
Renal Disease	5.06	
Rheumatic Disease	40.64	
Syncope	0.53	
Sleep Disorders		
Apnea	4.43	
Insomnia	1.19	
Mental Health		
Attention-Deficit/Hyperactivity Disorder	0.19	
Alcohol Use Disorder	3.49	
Anxiety	5.20	

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 5-5 Continued

Covariates	Percentage % (or mean)	Standard Deviation
Bipolar Disorder	1.57	
Depression	10.10	
Substance Use Disorder	1.77	
Opioid Overdose	0.01	
Posttraumatic Stress Disorder	9.43	
Schizophrenia and Psychosis	1.16	
Suicidal Ideation	0.26	
Traumatic Brain Injury	1.15	
Average Pain Intensity Rating (at baseline) (VHA Vital Signs data) (Range 1–10)	(4.50)	(2.86)
Pain Score at Baseline		
0	13.86	
1	3.75	
2	4.89	
3	6.58	
4	6.97	
5	7.52	
6	6.40	
7	6.50	
8	6.81	
9	3.35	
10	3.39	
Missing	29.97	
BMI		
Underweight	0.90	
Normal	17.80	
Overweight	32.30	
Obese	41.40	
Missing	7.60	
Health Care Coverage		
Supplemental Health Insurance to VHA Coverage	46.82	
Medicare (ever/never)	18.21	
Health Care Utilization in past year		
Number of VA Outpatient Visits		
VA Outpatient Visits (0–3)	16.33	
VA Outpatient Visits (4–11)	20.86	
VA Outpatient Visits (12–21)	20.00	
VA Outpatient Visits (22–42)	22.13	
VA Outpatient Visits (43–67)	10.56	
VA Outpatient Visits (68+)	10.11	

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 5-5 Continued

Covariates	Percentage % (or mean)	Standard Deviation
Inpatient Hospital Admission	0.07	
Nursing Home Visit		
Nursing Home Visit (Yes/No)	0.35	
Military Status		
Service Era		
Peacetime, only	24.12	
Vietnam	39.99	
Gulf War	18.66	
Korean War	7.89	
Multiple Eras	3.38	
WWII, only	5.00	
Missing	1.64	
Combat Service (yes/no)		
Combat Service	14.32	
Military Sexual Trauma, yes/no		
Military Sexual Trauma	5.00	
Military Branch	0.00	
Army	48.49	
Coast Guard	0.69	
Air Force	11.37	
Marines	8.27	
National Guard	0.01	
Navy	16.27	
Missing	14.87	
Prescription Information (dispensed within 90 days before baseline, Yes/No)		
Opioid Formulation		
Any Long Acting	1.00	
Benzo Co-Prescription (≥1 benzo tablet dispensed during episode month)	6.73	
Prescription Information (dispensed within 90 days before baseline, Yes/No)		
Gabapentinoids	5.82	
Anticonvulsant		
Carbamazepine	0.26	
Oxcarbazepine	0.06	
Topiramate	0.50	
Antidepressant	14.81	
Antihistamine		
Hydroxyzine	1.42	
Anxiolytic		
Buspirone	0.69	
Migraine Pharmacotherapy	1.50	

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 5-5 Continued

Covariates	Percentage % (or mean)	Standard Deviation
Muscle Relaxers	11.58	
NSAIDs[3]	74.30	
Acetaminophen	67.39	
Facility urbanicity		
Non-Core	22.83	
Micropolitan	7.54	
Small Metropolitan	11.84	
Medium Metropolitan	1.37	
Large Fringe Metropolitan	35.53	
Large Central Metropolitan	4.43	
Missing	15.88	

[1] Department of Veterans Affairs.
[2] COPD: chronic obstructive pulmonary disease.
[3] NSAID: Non-steroidal anti-inflammatory drugs.
NOTES: No cell sizes of 10 or less are included in the reported result. Baseline characteristics as well as missingness are not comparable across trials as the cohorts for each study are distinct, due to study specific differences in inclusion and exclusion criteria.

Table 5-6 presents the results of the primary G-formula modeling for the initial opioid dosage strategies (study 2a). Table 5-7 presents the results of the primary G-formula modeling for the dosage escalation strategies. Results for suicide mortality were not reported, given sample size constraints. Specifically, few suicide mortality events occurred before censoring due to stopping opioid pharmacotherapy, resulting in few observed suicide deaths while veterans were active in opioid treatment on which to base modeling.

See supplementary Table 5-8 for additional details on missingness.

DISCUSSION

This study estimated the effect of initial opioid dosages and dosage escalation over 6 months on mortality among veterans newly dispensed opioid pharmacotherapy. Several studies established an association of higher versus lower opioid dosages with all-cause mortality and suicide mortality (Binswanger et al., 2022; Kaplovitch et al., 2015; Gomes et al., 2011; Bohnert et al., 2011b; Dunn et al., 2010). Studies among veterans have particularly

TABLE 5-6 Study 2a. Among VHA Veterans Newly Dispensed Full-Agonist Opioid Pharmacotherapy, Estimated Risk of All-Cause Mortality and Risk Ratio By Initial Dosage (2007–2019; *N* = 5,639,108)

Initial dosage strategy[a] (MME/Day)	Risk Estimate (%)	Bootstrap Standard Error	95% CI[b]	Risk Ratio	95% CI[b]
Low (>0 to ≤20)	3.95	0.16	3.69–4.29	1.00 (Ref)	(Ref)
Medium (>20 to ≤40)	4.89	0.19	4.55–5.33	1.24	1.20–1.28
High >40 to ≤50)	5.80	0.19	5.44–6.24	1.47	1.44–1.50

[a] Initial dosage strategy is calculated as the average morphine milligram equivalent (MME)/day during the index month. The MME is a measure of the intensity of opioid exposure; it standardizes opioid prescriptions considering differences in the potency, quantity, and strength of different types of dispensed opioids. The committee calculated MMEs using CDC conversions.
[b] CIs were calculated using the percentile method from 400 bootstrap samples.
NOTES: No cell sizes of 10 or less are included in the reported result.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 5-7 Study 2b. Among VHA Veterans Newly Dispensed Full-Agonist Opioid Pharmacotherapy, Estimated Risk of All-Cause Mortality and Risk Ratio by Dosage Escalation Strategies (2007–2019; *N* = 5,639,108)

Dosage escalation strategy[a] (Average MME/Day change in 6 months)	**Risk Estimate (%)**	**Bootstrap Standard Error**	**95% CI**[b]	**Risk Ratio**	**95% CI**[b]
Stable (0 to <5)	2.70	0.18	2.34–3.08	1.00 (Ref)	(Ref)
Slow (≥5 to <10)	4.56	0.17	4.27–4.92	1.69	1.53–1.89
Fast (≥10 to <20)	4.69	0.17	4.39–5.06	1.74	1.57–1.94

[a] Dosage escalation strategy is calculated as the average morphine milligram equivalent (MME)/day change in 6 months. The MME is ideal to measure the intensity of opioid exposure; it standardizes opioid prescriptions considering differences in the potency, quantity, and strength of different types of dispensed opioids. The committee calculated MMEs using CDC conversions.

[b] CIs were calculated using the percentile method from 400 bootstrap samples.

NOTE: No cell sizes of 10 or less are included in the reported result.

shown that those who received higher opioid dosages for pain treatment had a higher risk of suicide and self-harm (Hayes et al., 2020; Ilgen et al., 2016). All of these earlier studies used conventional observational methods, whose designs (e.g., lack of a specific "time zero," time-anchor misalignment) may contribute to biases that can impact the results. The present study used methods designed to estimate causal effects from observational data.

One key difference between this study and others was the use of G-formula methods to handle complex time-varying confounding. A second key difference was the committee's application of a new user design to improve the rigor of the design and validity of comparisons. Because several years typically pass before individuals escalate to very high dosages, the new user design inherently limited the highest dosage levels that could be examined in the present study.

In a well-powered nested case-control study from Canada, MME/day levels of 20–100 were associated with odds ratios of 1.32–2.04 for the outcome of all-cause mortality, compared to MME/day levels of 1–19 (Gomes et al., 2011). These dosage levels are similar to those that may be achieved after 6 months under the initial dosage and dosage escalation strategies examined in the present study, and the dosage levels of the comparator groups are also similar between studies. Although improved methods to ensure comparability between treatments (i.e., dosage levels) may also explain some of the smaller effect sizes for the present study compared to this and other studies, the findings are generally consistent with one another. However, the present study findings suggested a threshold effect after which faster dosage escalation does not confer greater risk of death, whereas other studies focused on overdose-mortality specifically have generally found dose–response effects (Gomes et al., 2011).

The findings from this analysis should be considered in light of some limitations. First, only veterans who were newly dispensed full-agonist opioid pharmacotherapy were included; therefore, the findings may not generalize to veterans who initiated partial agonist opioid pharmacotherapy (e.g., buprenorphine), which can also be used to treat pain. Second, given that the committee did not have access to other sources of pharmacy data, such as from the DoD or other private payers (commercial, TRICARE, self-pay), there will be some uncertainty that the study 2 population were truly opioid naïve. However, with the available pharmacy data, the committee applied exclusion criteria to capture at best a truly opioid-naïve study population. Third, different approaches for estimating opioid dosages have been proposed in the literature, each with pros and cons (Dasgupta et al., 2021). The committee's approach for measuring opioid dosages captures the average over time and does not indicate cumulative opioid exposure or exact dosages that preceded mortality. Fourth, as noted, the committee focused on dosage trajectories over a relatively short time span, which limits comparability to studies examining very high dosages (e.g., 100+ MME) or dosage differences occurring well into treatment (Dasgupta et al., 2021). The committee made these choices to adhere to TTE framework practices (e.g., new users). Fifth, given the application of G-formula, the share of risk attributable to the initial dosage versus the escalation trajectory, or the combined effect of these two aspects of treatment, could not be reported. Sixth, the number of suicide deaths precluded the ability to report results for the association of initial opioid dosages and escalation strategies with suicide mortality. Additionally,

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the computing constraints and sample size within many subgroups also forestalled any subgroup and sensitivity analyses. Nonetheless, the reported risks, RRs, and confidence intervals still provide important information in response to the statement of task. It is evident from the findings that the risk for all-cause mortality increases with higher initial dosages and faster dosage escalation trajectories. Seventh, there is always the potential for residual confounding in an observational study, and the high amount of missing data on time-varying pain intensity ratings may contribute to missed measurement of key confounding variables. Lastly, the potential for positivity assumption[15] violations cannot be ruled out because the committee used fairly strict dosage trajectory definitions and many covariates; therefore, the number of individuals with a given set of covariates and treatment patterns would be small. The committee sought to identify the causal effect of different dosage escalation strategies on mortality. A large number of potential dosage trajectories occur in practice, but treatment patterns were selected to ensure contrast between treatments and interpretability of results. Because of the wide array of actual trajectories, few individuals adhered strictly, and the inferences rely on some degree of extrapolation.

FINDINGS

The committee was tasked with quantifying the causal effect of different initial opioid dosage and escalation strategies on the risk of death among veterans who received care from the VHA between 2007–2019; the committee addressed this component of the statement of task using TTE. Study 2 addresses the objective outlined in part (b) of the statement of task, which is to examine "the effect of higher doses relative to lower doses of opioids."

Finding 2a-1. Among veterans with newly dispensed opioid pharmacotherapy, the 12-month risk of all-cause mortality in each of the initial opioid dosage strategy was 3.95 percent for low, 4.89 percent for medium, and 5.80 percent for high. ($RR_{medium\ vs\ low}$: 1.24 [95% CI: 1.20–1.28] and $RR_{high\ vs\ low}$: 1.47 [95% CI: 1.44–1.50]).

Finding 2a-2. Among veterans with newly dispensed opioid pharmacotherapy, the committee is unable to draw conclusions about the effect of those who received a high or medium initial daily opioid dosage level, compared to veterans with a low initial daily opioid dosage level on suicide mortality within 12 months of follow-up, due to the lower number of suicide deaths in the eligible population.

The estimated mortality risk ranged from 3.95 percent in the low dosage strategy to 5.80 percent in the high dosage strategy. The estimated RRs, using the low dose strategy as the reference, suggest that mortality rates were higher for the medium (1.24) and high dosage (1.47) strategies.

Finding 2b-1. Among veterans with newly dispensed opioid pharmacotherapy, the 12-month risk of all-cause mortality in each of the dosage escalation strategy was 2.70 percent for stable, 4.56 percent for slow, and 4.69 percent for fast over the first 6 months. ($RR_{slow\ vs\ stable}$: 1.69 [95% CI: 1.53–1.89] and $RR_{fast\ vs\ stable}$: 1.74 [95% CI: 1.57–1.94]).

Finding 2b-2. The committee is unable to draw conclusions about the effect of escalating dosages of opioid pharmacotherapy on suicide mortality within 12 months of follow-up, due to the lower number of suicide deaths in the eligible population.

CONCLUSIONS

The committee evaluated the effect of different opioid dosage strategies on all-cause mortality and suicide mortality. The committee employed the TTE framework to reduce biases, such as due to immortal time, and confounding. In addition, the committee leveraged the large observational datasets (e.g., health care, clinical, and

[15] Positivity is an assumption that all types of individuals must have the possibility of following each treatment protocol. In this study, a violation could occur when some individuals are not observed to receive one of the dosage trajectories.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

administrative data) available within the VA and VHA, supplemented by CMS data, and the NDI for mortality data. Based on the study findings, the committee makes the following conclusions for veterans who received care from the VHA between 2007–2019:

Conclusion 3. The committee concludes that there is an increased risk of all-cause mortality among veterans who initiated opioid treatment at higher dosage levels compared to lower levels.

Conclusion 4. The committee concludes that there is an increased risk of all-cause mortality among veterans whose treatment strategy was either slow or fast opioid dosage escalation compared to stable dosage.

Conclusion 8. Given the lower number of suicide deaths in the eligible population the committee is unable to conduct analyses to address the question of the effect of different opioid dosage treatment strategies on suicide mortality.

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ANNEX: SUPPLEMENTARY FIGURES AND TABLES

TABLE 5-8 Missing Percentages of Variables in the Model. Among VHA Veterans Newly Dispensed Full-Agonist Opioid Pharmacotherapy, Missingness of Variables Included in the Current Analysis (2007–2019; *N* = 5,639,108)

Covariate	% Missing
Sex	0.00
Age (Continuous)	0.00
Race	9.79
Ethnicity	5.86
Marital Status	5.47
Disability Status	0.27
History of homelessness (yes/no)	0.00
Tobacco Use Ever (Yes/No)	0.00
Health Conditions	
Physical Health Conditions	
Abdominal pain	0.00
Back Pain	0.00
Fibromyalgia	0.00
Fractures	0.00
Headaches	0.00
Limb Pain	0.00
Musculoskeletal Pain	0.00
Neck Pain	0.00
Neuropathy	0.00
Orofacial Pain	0.00
Systemic Disorders	0.00
Urogenital Pain	0.00
Other	0.00
AIDS/HIV	0.00
Blood Loss Anemia	0.00
Cardiovascular Disease	0.00
Cerebrovascular Disease	0.00
Chronic Lung Disease	0.00
Cirrhosis	0.00
COPD[1]	0.00
Deficiency Anemia	0.00
Dementia	0.00
Diabetes	0.00
End Stage Renal Disease	0.00
Heart Disease	0.00
Hepatitis	0.00
Hemiplegia or Paraplegia	0.00
Liver Disease	0.00

continued

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Table 5-8 Continued

Covariate	% Missing
Migraine	0.00
Peptic Ulcer Disease	0.00
Peripheral Vascular Disease	0.00
Pulmonary Circulation Disorders	0.00
Renal Disease	0.00
Rheumatic Disease	0.00
Syncope	0.00
Sleep Disorders	
Apnea	0.00
Insomnia	0.00
Mental Health	
Attention-Deficit/Hyperactivity Disorder	0.00
Alcohol Use Disorder	0.00
Anxiety	0.00
Bipolar Disorder	0.00
Depression	0.00
Drug Use Disorder	0.00
Opioid Overdose	0.00
Posttraumatic Stress Disorder	0.00
Schizophrenia and Psychosis	0.00
Suicidal Ideation	0.00
Traumatic Brain Injury	0.00
Average Pain Intensity Rating (in past month)	29.97
Body Mass Index	7.64
Health Care Coverage	
Supplemental Health Insurance to VHA Coverage	0.03
Medicare (ever/never)	0.00
Health Care Utilization in Past Year	
Number of VA[2] Outpatient Visits	0.00
Inpatient Hospital Admission	0.00
Nursing Home Visit (Yes/No)	0.00
Military Status	
Service Era	1.64
Combat Service	0.00
Military Sexual Trauma	2.25
Military Branch	14.87
Prescription Information	
Opioid Formulation	
Any Long Acting	0.00
Benzo Co-Prescription (≥1 dispensed tablet during episode month)	0.00

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Table 5-8 Continued

Covariate	% Missing
Prescription Information (Rx[3] dispensed within 90 days before baseline, Yes/No)	
Gabapentinoids	0.00
Anticonvulsant	
Carbamazepine	0.00
Oxcarbazepine	0.00
Topiramate	0.00
Antidepressant	0.00
Desvenlafaxine	0.00
Mirtazapine	0.00
Venlafaxine	0.00
Antihistamine	
Hydroxyzine	0.00
Anxiolytic	
Buspirone	0.00
Migraine Pharmacotherapy	0.00
Muscle Relaxers	0.00
Other Non-Opioid Analgesic	
Acetaminophen	0.00
Facility urbanicity	15.88

[1] COPD: Chronic obstructive pulmonary disease.
[2] VA: Veterans Affairs.
[3] Rx: Prescription.
NOTE: No cell sizes of 10 or less are included in the reported result.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

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6

The Effect of Benzodiazepine Co-Prescribing[1] on All-Cause Mortality, Including Suicide Mortality, Among Individuals on Consistent Opioid Pharmacotherapy

INTRODUCTION

The studies explored in the previous two chapters compared the effect of newly dispensed[2] opioid pharmacotherapy compared to non-opioid pain pharmacotherapy on all-cause mortality and suicide mortality in individuals who are opioid naïve (Chapter 4), as well as the effects of initial opioid dosage and dosage escalation strategies in opioid-naïve individuals on all-cause mortality and suicide mortality (Chapter 5). However, among individuals consistently dispensed opioid pharmacotherapy, or long-term opioid treatment (LTOT), the prescribing of other pharmacotherapies for the treatment of co-occurring physical and mental health conditions may increase the risk of harm. Of particular concern to individuals, clinicians, and policy makers is the potential for harm when individuals receiving consistent LTOT are prescribed benzodiazepine pharmacotherapy. In this chapter, the committee focused on the effect of newly dispensed benzodiazepine pharmacotherapy compared to alternative non-benzodiazepine pharmacotherapy in individuals consistently dispensed opioid pharmacotherapy on all-cause mortality and suicide mortality. The committee identified alternative non-benzodiazepine pharmacotherapy as those that treat insomnia or anxiety.

Clinical Use of Benzodiazepine Pharmacotherapy

Benzodiazepines are prescription sedatives typically used to treat anxiety, insomnia, panic disorders, alcohol withdrawal, seizures, and muscle spasms as well as for sedation in the perioperative period (DEA, 2020; FDA, 2020; Lembke et al., 2018; Olfson et al., 2015). As of 2020, the Food and Drug Administration (FDA) approved (on-label use) select benzodiazepines in clinical settings to treat generalized anxiety disorder (GAD), insomnia, seizures, social phobia, and panic disorder (FDA, 2020). Some benzodiazepines, such as diazepam, lorazepam, and clonazepam, are not FDA approved for GAD in adults, but they are frequently used off label for this purpose (Strawn et al., 2018). Similarly, other select benzodiazepines associated with sedative and hypnotic effects (including clonazepam and lorazepam) are frequently used off label to treat adult insomnia (Ghiasi et al., 2024; Basit and Kahwaji, 2023; Madari et al., 2021). Similar to opioids, benzodiazepines can cause mild to severe depression

[1] Operationalized as co-dispensing in the analysis.

[2] In the committee's studies "newly dispensed" was defined as pharmacotherapy of interest not previously dispensed to the individual in the last 90 days before the start date.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

of the central nervous system (see Box 1-1). Long-term use of benzodiazepines can lead to an increased tolerance and the need for higher dosages, contributing to dependence and the potential development of a substance use disorder (Fluyau et al., 2018). However, short-term exposure to benzodiazepines, or changes in dose, may have adverse effects related to respiratory depression and oversedation. When combined with other prescribed pharmacotherapies, short-term use of benzodiazepines can have adverse effects resulting in death (Hernandez et al., 2018; Passaro et al., 2000).

Prescribing Benzodiazepine Pharmacotherapy

The percentage of U.S. adults prescribed benzodiazepines increased during the study 3 period (2007–2019). Based on an analysis of the Medical Expenditure Panel Survey, the proportion of adults with a filled benzodiazepine prescription increased from 4.1 percent in 1996 to 5.6 in 2013 (Bachhuber et al., 2016). Moreover, data from the National Ambulatory Medical Care Survey showed a marked increase in the proportion of individuals prescribed benzodiazepines in the outpatient setting, from 3.8 percent in 2003 to 7.4 in 2015 (Agarwal and Landon, 2019). An analysis of 2015–2016 data from the National Survey on Drug Use and Health found that 12.6 percent of U.S. adults reported benzodiazepine use in the past year (Maust et al., 2019). Toward the end of the study 3 period and beyond, 2017–2021, benzodiazepine dispensing rates declined—from 31.2 per 100 persons in 2017 to 25.8 per 100 persons in 2021.[3]

Risks Associated with Benzodiazepine Use

Risks associated with benzodiazepines include deaths due to overdose and suicide, as well as falls, fractures, cognitive dysfunction, motor vehicle crashes, non-fatal overdose, anterograde amnesia, of which older individuals are especially at increased risk (Edinoff et al., 2021; AGS, 2019; Dodds, 2017; Glass et al., 2005; Stewart, 2005; Cumming and Couteur, 2003; Wang et al., 2001; Hemmelgarn et al., 1997; Ray et al., 1992; Curran, 1991). Furthermore, chronic benzodiazepine use is associated with an elevated risk of dementia and Alzheimer's disease (de Gage et al., 2014, 2012). Additionally, Kripke and colleagues (2012) reported greater than a threefold increase in likelihood of mortality among individuals taking benzodiazepines and other hypnotics.

Further, although clinical guidelines of the American Geriatrics Society recommend that older adults avoid benzodiazepines, studies continue to demonstrate that use of benzodiazepines was about three times more prevalent in adults over 50 compared to younger adults (AGS, 2019; Maust et al., 2019; Olfson et al., 2015; Wysowski and Baum, 1991).

Data from the Centers for Disease Control and Prevention (CDC) highlights that benzodiazepine-related drug overdose deaths increased from 1,135 in 1999 to 11,537 in 2017 and declined to 9,711 in 2019 (NIDA, 2023). Between 2019 and 2021, deaths rose again to 12,499 before beginning to decline again in 2022 (NIDA, 2023). In overdose deaths with benzodiazepines and opioids (2000–2019), 86.2 percent were classified as accidental, 8.5 percent as suicides, and 5.2 percent as undetermined intent (Kleinman and Weiss, 2022). Among overdose deaths involving benzodiazepines, 55.9 percent were classified as accidental, 36.2 percent as due to suicide, and 7.7 percent as underdetermined intent (Kleinman and Weiss, 2022). Overdose deaths with both benzodiazepines and antidepressants (e.g., tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, and other unspecified antidepressants) were categorized as suicide in 51.4 percent of cases from 2000–2019 (Kleinman and Weiss, 2022).

Alternative Pharmacotherapies to Benzodiazepines

Alternative pharmacotherapies for anxiety, insomnia, and other indications for benzodiazepines include TCAs, tetracyclic antidepressants (TeCAs), serotonin-norepinephrine reuptake inhibitor (SNRIs), buspirone, and selective serotonin reuptake inhibitors, which are sometimes used to treat depression, anxiety, and other mental health conditions (Garakani et al., 2020; Krystal et al., 2019; Dale et al., 2015; Bespalov et al., 2009; Wilson and Nutt, 2007).

[3] Dr. Christopher Jones. Presentation to the committee on March 9, 2023. Trends in Opioid and Benzodiazepine Use, Misuse, and Overdose.

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Concomitant Use of Opioids and Benzodiazepines

Concomitant use of opioids and benzodiazepines can have significant adverse effects. This section highlights trends and studies that examine this co-prescribing in the general population and its potential risks.

Trends in Private-Sector Co-Prescribed Opioids and Benzodiazepines

Before release of the 2016 CDC Clinical Practice Guidelines (CPGs) for Prescribing Opioids for Pain, co-prescription of opioids and benzodiazepines was increasing nationally, affecting a sizable percentage of individuals between 2001–2010. Data from the National Ambulatory Medical Care Survey/National Hospital Ambulatory Medical Care Survey showed that benzodiazepines and opioids were co-prescribed at 8.1 percent of acute pain visits and 15.5 percent of chronic pain visits (Larochelle et al., 2015). In a study examining more than 300,000 continuously insured individuals receiving opioid prescriptions between 2001 and 2013, the percentage of persons also receiving prescribed benzodiazepines increased from 9.0 percent in 2001 to 17.0 in 2013 (Sun et al., 2017). Analysis of data from the National Health and Nutrition Examination Survey (NHANES) showed that co-prescribing increased from 11.5 percent in 2007–2008 to 16.1 in 2013–2014, decreased to 15.0 percent in 2015–2016, and then decreased further to 8.7 percent in 2017–2018 (Rhee et al., 2021). A decrease in the percentage of individuals with concurrent prescriptions of both benzodiazepines and opioids was also observed in claims data from both commercial insurance and Medicare Advantage following the release of the CDC guidelines in 2016 (Jeffery et al., 2019).

Adverse Outcomes Associated with Opioid and Benzodiazepine Co-Prescribing

Long-term opioid and benzodiazepine treatment, both independently and together, is associated with adverse outcomes and all-cause mortality, including deaths due to accidents, suicide, and overdose, regardless of misuse (VA/DoD, 2022; Gibbons et al., 2021; Xu et al., 2020; Bohnert and Ilgen, 2019; Votaw, 2019; Gressler et al., 2018; VA/DoD, 2017; Sun et al., 2017; Park et al., 2015). Adverse outcomes associated with the concomitant use of benzodiazepines and opioids include an increased risk of overdose (Bachhuber et al., 2016; Park et al., 2015; Sharp and Melnik, 2015; Turner and Liang, 2015; Chen et al., 2014), suicide (Pfeiffer et al., 2009), and all-cause mortality (Xu et al., 2020; Gaither et al., 2016; Weich et al., 2014); the use of emergency services (Yarborough et al., 2019; Sun et al., 2017; Nielsen et al., 2015); and number of serious emergency department visits (e.g., hospitalization or death) (Yarborough et al., 2019; Kaufmann et al., 2017; Jones and McAninch, 2015; Day, 2014). Furthermore, concomitant use of benzodiazepines and opioids can cause a synergistic effect that augments the opioids' euphoric effects in the brain, potentially increasing risk of addiction and subsequent adverse effects (Jones et al., 2012; Lintzeris and Nielsen, 2010).

All-Cause Mortality. The concomitant use of benzodiazepines and opioids has been found to further suppress respiratory drive (the intensity of the respiratory system output, which results in breathing [Jonkman et al., 2020]), a common cause of death from opioid overdose, and compound each medication's independent adverse effects that increase risk for all-cause mortality (Xu et al., 2020; White and Irvine, 1999). A study using NHANES and National Death Index (NDI) data, and with a reference comparator group of those prescribed selective-serotonin reuptake inhibitors, Xu and colleagues (2020) found a higher risk for all-cause mortality in those with concomitant use of prescribed benzodiazepines and opioids (hazards ratio (HR): 2.04; 95% CI: 1.65–2.52) and those prescribed only benzodiazepines (HR: 1.60; 95% CI: 1.33–1.92).

Suicide Mortality. Suicide and overdose mortality are of particular concern with concurrent prescription of opioids and benzodiazepines (Xu et al., 2020; White and Irvine, 1999). This combination of pharmacotherapy can have adverse effects given that opioid-induced respiratory depression. The sedating effects of benzodiazepines can further suppress breathing and increase the risk for fatal overdose and mortality. However, there are challenges in distinguishing between overdose mortality and deaths due to suicide as intentional or accidental, as well as challenges in attributing the cause of death to one medication or another (Hedegaard et al., 2018). These challenges complicate the ability to reliably infer which pharmacotherapy was the leading contributor to mortality and understand if

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

overdose was intentional or unintentional in both the clinical setting and observational studies. Most studies described in the next section report on overdose mortality.

A high percentage of overdose deaths are associated with both benzodiazepines and opioids. Of 118,208 U.S. benzodiazepine-related overdose deaths between 2000–2019, 83.5 percent were associated with opioids (Kleinman and Weiss, 2022). A 2014 report referencing data from the National Vital Statistics System reported that benzodiazepines were involved in 31 percent of the opioid-analgesic poisoning deaths in 2011 (Chen et al., 2014). Based on the number of national drug overdose deaths, in 2018, about 20 percent of overdose deaths involving opioids also involved benzodiazepines (NIDA, 2023). By 2021, 14 percent of overdose deaths involved both opioids and benzodiazepines (NIDA, 2023). Another study based on state-controlled substance prescription drug monitoring program data demonstrated a 10 times higher risk of death from overdose among individuals receiving concomitant opioid and benzodiazepine in the past year compared to those who received only opioids (Dasgupta et al., 2016).

A study using Veteran Health Administration (VHA) data from 2004 to 2009 found that approximately 50 percent of the veterans receiving opioids who died from overdose had a concurrent benzodiazepine prescription (Park et al., 2015). From 1996 to 2010, the rate of benzodiazepine overdose deaths per 100,000 U.S. adults increased fourfold; this rate then plateaued from 2010 to 2013 (Bachhuber et al., 2016). Opioid-involved benzodiazepine overdose deaths increased from 2000 to 2017 (0.32 per 100,000 to 3.08 per 100,000) and then decreased in 2019 to 2.53 per 100,000 in the United States (Kleinman and Weiss, 2022). Between 2000 and 2019, 118,208 benzodiazepine-involved overdose deaths occurred, with opioids co-involved in 83.5 percent of the deaths. Of overdose deaths co-involving opioids and benzodiazepines, 86.2 percent were classified as accidental, 8.5 percent as suicide, and 5.2 percent as undetermined intent. In 2019, 53.3 percent of benzodiazepine-involved overdose deaths co-involved synthetic opioids, 34.6 percent co-involved natural and semisynthetic opioids, and 21.1 percent co-involved heroin (Kleinman and Weiss, 2022).

Based on 2013–2014 Medicare Part D data, Hernandez and colleagues (2018) found that during the first 90 days of concurrent opioid and benzodiazepine use, opioid-related overdose risk was five times higher than among those using opioids only. However, after 180 days, the overdose risk was similar between the two groups.

Guidelines on Concomitant Prescription of Opioids and Benzodiazepines

Before 2016, no explicit contraindication guidelines existed for co-prescribing opioids and benzodiazepines (an earlier VA/Department of Defense (DoD) CPG provided guidance on co-prescribing benzodiazepines with methadone and fentanyl, specifically) (VA/DoD, 2010). In 2016, the FDA added a black box warning (its highest safety warning) to benzodiazepines, opioids, and opioid-containing cough medicines indicating the dangers of independent and combined use (FDA, 2016). Subsequent CPGs, 2016 U.S. CDC CPG and the 2017 VA/DoD CPG for the Management of Opioid Therapy for Chronic Pain (last updated in 2022), included strong, evidence-based recommendations to not co-prescribe any opioid with any benzodiazepine. Additionally, the Centers for Medicare & Medicaid Services (CMS) has raised concerns and explicitly recommended against concurrent use (CMS, 2019).

As noted, there are many potential clinical reasons for co-prescribing opioids and benzodiazepines, such as the co-occurrence of anxiety and other mental health conditions, sleep disturbance in individuals experiencing pain, the cyclical and compounding effect of mental health conditions on pain, and short-term needs (e.g., dental visits, magnetic resonance imaging (MRI)) (Hirschtritt et al., 2021; Quagliato et al., 2018; Kroenke et al., 2011; Tunks et al., 2008; Chou, 2007; McWilliams et al., 2003). Hawkins and colleagues (2017) conducted a survey among prescribers to understand decision making behind co-prescribing benzodiazepines and opioids among veterans receiving care from the VHA. The study results identified several factors that contributed to co-prescribing: lack of information among providers regarding other treatments, lack of information regarding individual behavior with other treatments, insufficient time to discuss discontinuation of one of the medications, and the view that discontinuation of benzodiazepines would both be too difficult and contribute to individual discomfort (Hawkins et al., 2017).

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

STUDY 3 METHODS

Study 3 aimed to answer the following research question: among veterans receiving care in the VHA who were consistently[4] dispensed[5] opioid pharmacotherapy between 2007 and 2019, what is the effect of newly dispensed benzodiazepine versus alternative non-benzodiazepine pharmacotherapy for anxiety and other common indications for benzodiazepines on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) within a 3-month follow-up period?

The committee designed this observational analysis to emulate a target trial estimating the effect of benzodiazepine pharmacotherapy compared with alternative non-benzodiazepine pharmacotherapy on all-cause mortality and suicide mortality among those who were consistently dispensed opioid pharmacotherapy. A target trial is the hypothetical randomized pragmatic trial that would have best answered the causal question. Target trial emulation (TTE) framework includes two steps: (1) specify the protocol of the target trial, and (2) specify how the target trial will be emulated using observational data. The TTE framework is useful because it helps to ensure comparison of realistic treatment strategies, avoids biases from misalignment of time anchors (time zero/index date), and uses enhanced statistical techniques for minimizing confounding (Gomes et al., 2022; Hernán and Robins, 2016).

The protocol and specifications of the target trial (study 3) and how the committee emulated the target trial in the observational data are described in the following subsection and summarized in Table 6-1.

In addition, given the complexity of each study, the committee developed Figure 6-1, which reflects key temporal aspects of the longitudinal study design, specifically the index or date of entry into the study, exposure washout period, windows for exclusion and covariate assessments, and follow-up time (Schneewiss et al., 2019).

Study Population and Data Sources

The study population is defined as veterans receiving care in the VHA, and the study period is from January 1, 2007, to December 31, 2019.[6] The earliest index date, or start date, was January 1, 2007.[7] The latest possible index date was October 1, 2019, to allow individuals to be followed for 3 months after a newly dispensed benzodiazepine or alternative non-benzodiazepine pharmacotherapy. To assess exclusion and eligibility in the study and follow-up, data from 2006–2019 were pulled for analyses.

Data from the national VHA data files were linked to the Department of Veterans Affairs (VA) Corporate Data Warehouse (CDW), U.S. Veterans Eligibility Trends and Statistics, NDI, and Medicare Part A, B, C, and D data from the CMS. Primary sources for individual inclusion/exclusion and covariates were VA and VHA data. CMS data were used to supplement individual data used for inclusion/exclusion and other covariates. Data files were linked based on a combination of a veteran's unique individual integrated control number, Social Security number (SSN), and date of birth. The National Academies of Sciences, Engineering, and Medicine Institutional Review Board approved the study.

SPECIFICATIONS FOR THE EMULATED TARGET TRIAL 3

Drawing from this study population of all veterans who received care in VHA facilities, this study focused on a population consistently dispensed opioid pharmacotherapy that were newly dispensed either a benzodiazepine or an alternative non-benzodiazepine pharmacotherapy. Figure 6-2 illustrates the flowchart detailing the selection process of including eligible veterans in study 3. The following sections outline each of the target trial components for study 3.

[4] The committee defined as three or more dispensed opioids at least 21 days apart within a 180-day period for at least 84-day supply or two dispensed opioids of 90-day supply within 180 days.

[5] The committee notes differences in types of pharmacy data measures. Pharmacy data can be categorized into three measures: *prescribed* (prescriber submits a prescription to a pharmacy), a *fill* (pharmacy completes the requested prescription), and *dispensed* (individual picks up/is mailed the prescription from the pharmacy). The committee used dispensed pharmacy data in its analyses. The committee operationalized the term "initiation" in the statement of task as "newly dispensed" pharmacotherapy in analyses.

[6] Latest possible index date was October 1, 2019, in study 3.

[7] Given that the earliest index date is January 1, 2007, the earliest pre-index data are January 1, 2006.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 6-1 Specifications for Study 3 Target Trial Protocol

Protocol Component	Target Trial Specification	Target Trial Emulation
Eligibility Criteria	• U.S. veteran • Age ≥18 years • Valid Social Security number • At least one encounter in VHA during 2007–2019 • No benzodiazepine or alternative non-benzodiazepine pharmacotherapies in the 90-day pre-index period • First eligible dispensed benzodiazepine or alternative non-benzodiazepine pharmacotherapy before October 1, 2019 • *Qualifying Opioid History at baseline:* ≥3 dispensed opioid prescriptions within a 180-day window with (1) ≥two 21-day gaps between prescriptions and (2) an 84+ day supply within the 180-day window. OR Two 90-day dispensed opioid prescriptions within 180-day window Exclusion: • ≥ 1 encounter or dispensed pharmacotherapy in Guam, Manila, Singapore VA facilities • At least one qualifying dispensed prescriptions of both benzodiazepine and alternative non-benzodiazepine pharmacotherapies within the same episode • Hospice/palliative care within past 12 months of index date • Cancer diagnosis (except non-melanoma skin cancers) within past 12 months • ≥ 1 dispensed medication for opioid use disorder (MOUD)[1] in 90-day pre-index Baseline is defined at the first month in which all eligibility criteria are met.	Same as target trial
Treatment strategies	Each individual is randomly assigned to one of the following treatment strategies, initiated at baseline only: 1. Initiate benzodiazepine pharmacotherapy (≥1 tablet) 2. Initiate alternative non-benzodiazepine pharmacotherapy (≥1 tablet)	Same as target trial Defined the date of pharmacotherapy initiation to be the first date of a dispensed pharmacotherapy.
Treatment Assignment	Individuals are randomly assigned to a strategy at baseline and are aware of their assigned strategy	Assumed randomized conditional on baseline covariates (sociodemographics, health conditions and behaviors, supplemental health insurance to VHA coverage, health care utilization, specific pharmacotherapies, facility, facility-level characteristic, and calendar month of eligible dispensed pharmacotherapy)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 6-1 Continued

Protocol Component	Target Trial Specification	Target Trial Emulation
Outcomes	Primary: All-cause mortality Secondary: Suicide mortality	Same as target trial
Start and End of Follow-Up	For each individual, follow-up starts at strategy assignment or treatment initiation (baseline). Eligible individuals are followed until death (or death due to other causes, in analyses of suicide mortality), or administrative end of follow-up at 3 months, whichever happens first.	Same as target trial
Causal Contrast	Intent-to-treat (ITT)[2] effect	ITT effect
Statistical Analysis	ITT analysis using IPTW	Observational analog of ITT effect.
	Subgroup analysis by age, sex, race, ethnicity, payment source for dispensed pharmacotherapy, time period). Sensitivity analysis: 1. 12-month follow-up period 2. Qualifying tablet quantity of ≥5 for benzodiazepine or alternative non-benzodiazepine pharmacotherapy	Same subgroup and sensitivity analyses.

[1] MOUD formulation of buprenorphine, methadone, naltrexone or LAAM.
SOURCE: Adapted from Hernán and Robins, 2016 and NASEM, 2019.

Study 3 Eligibility Criteria

For each calendar month from January 1, 2007, to December 31, 2019, the committee identified eligible individuals who met the following criteria: (1) be a U.S. veteran, (2) be 18 years or older, (3) have a valid SSN, and (4) have at least 1-year continuous enrollment in the VHA between 2006–2019, defined as at least one encounter in the VHA in the 12-month pre-index period. Eligible individuals also included veterans with at least one encounter in the VHA in the 12-month before index date within the eligible study period but only had a pharmacy claim through Medicare Part D (no VHA pharmacy claim). In addition, those who were eligible did not have an encounter or dispensed pharmacotherapy in Guam, Manila, or Singapore VHA facilities. These veterans were excluded because mortality data collected in these regions do not appear in the NDI data. See "exclusion criteria" for further information.

To be eligible for study 3, and similar to a prior analysis (Larochelle et al., 2022), VHA veterans had to be consistently dispensed opioid pharmacotherapy (defined as three or more dispensed opioids at least 21 days apart within a 180-day period for at least 84-day supply or two dispensed opioids of 90-day supply within 180 days) and have no dispensed benzodiazepine or an alternative non-benzodiazepine pharmacotherapy (see *Selection of Pharmacotherapies of Interest* section for more details on the committee's approach in selecting alternative non-benzodiazepine pharmacotherapies) in the 90-day pre-index period (the washout period). The committee established the 90-day washout period as the maximum duration of any dispensed prescription in the VHA is 90 days (except in rare circumstances [e.g., hospice]) (VHA, 2006).

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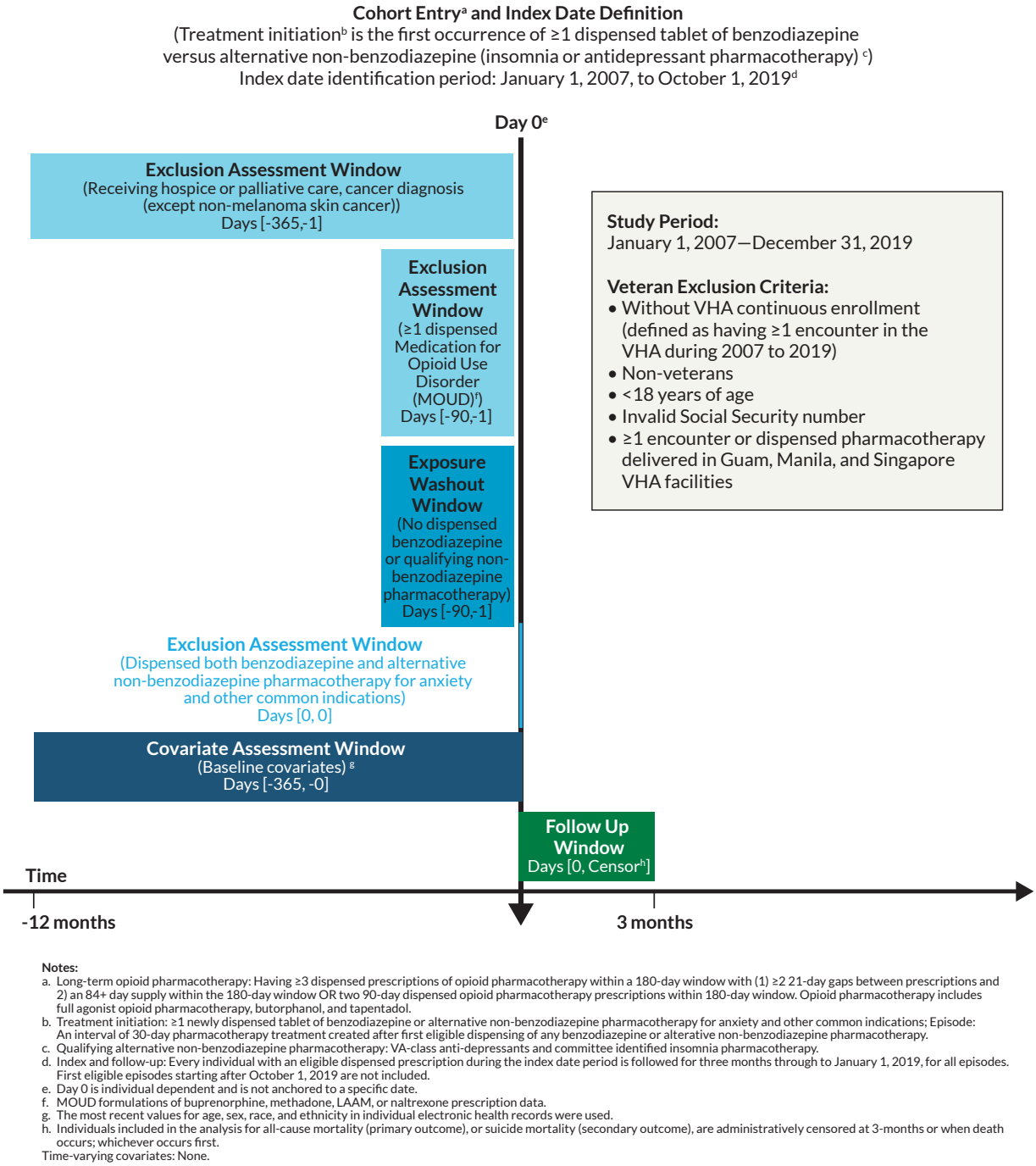

Notes:
a. Long-term opioid pharmacotherapy: Having ≥3 dispensed prescriptions of opioid pharmacotherapy within a 180-day window with (1) ≥2 21-day gaps between prescriptions and 2) an 84+ day supply within the 180-day window OR two 90-day dispensed opioid pharmacotherapy prescriptions within 180-day window. Opioid pharmacotherapy includes full agonist opioid pharmacotherapy, butorphanol, and tapentadol.
b. Treatment initiation: ≥1 newly dispensed tablet of benzodiazepine or alternative non-benzodiazepine pharmacotherapy for anxiety and other common indications; Episode: An interval of 30-day pharmacotherapy treatment created after first eligible dispensing of any benzodiazepine or alterative non-benzodiazepine pharmacotherapy.
c. Qualifying alternative non-benzodiazepine pharmacotherapy: VA-class anti-depressants and committee identified insomnia pharmacotherapy.
d. Index and follow-up: Every individual with an eligible dispensed prescription during the index date period is followed for three months through to January 1, 2019, for all episodes. First eligible episodes starting after October 1, 2019 are not included.
e. Day 0 is individual dependent and is not anchored to a specific date.
f. MOUD formulations of buprenorphine, methadone, LAAM, or naltrexone prescription data.
g. The most recent values for age, sex, race, and ethnicity in individual electronic health records were used.
h. Individuals included in the analysis for all-cause mortality (primary outcome), or suicide mortality (secondary outcome), are administratively censored at 3-months or when death occurs; whichever occurs first.
Time-varying covariates: None.

FIGURE 6-1 Study 3 design.
NOTE: No cell sizes of 10 or less are included in the reported result.

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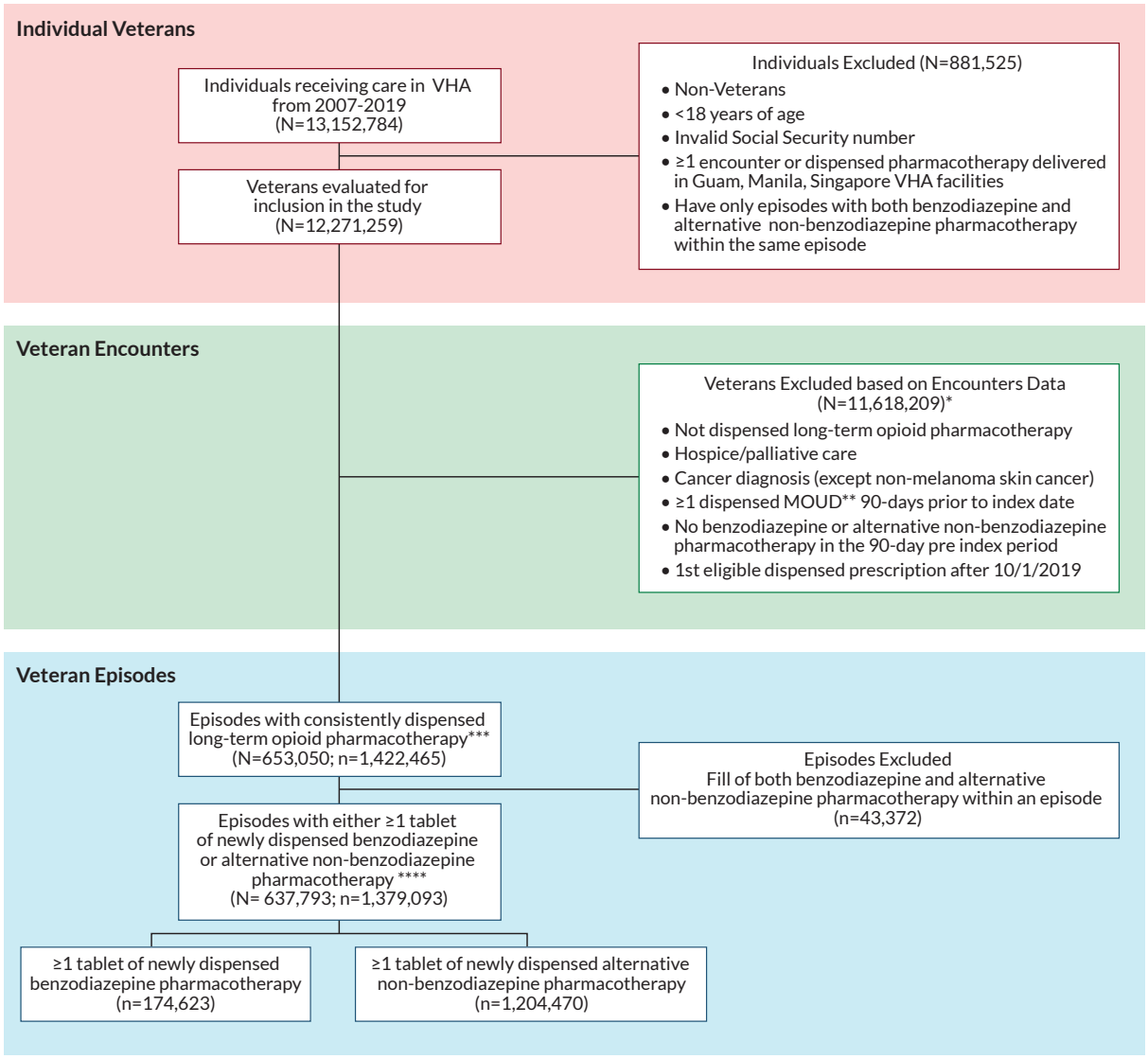

Note:
* Exclusions made prior to baseline (at 12 months, unless indicated otherwise) and not based on post-baseline information. See also Figure 6-1 exclusion assessment windows for timing information.
**Includes dispensed MOUD formulations of buprenorphine, methadone, LAAM, or naltrexone from prescription data.
*** Long-term opioid pharmacotherapy defined as: must receive ≥3 dispensed opioid pharmacotherapy prescriptions within a 180-day window with (1) ≥ two 21-day gaps between prescriptions and (2) an 84+ day supply within the 180-day window. OR Two 90-day dispensed opioid pharmacotherapy prescriptions within 180-day window.
**** Qualifying alternative non-benzodiazepine pharmacotherapy: VA-class anti-depressants and committee identified insomnia pharmacotherapy.

FIGURE 6-2 Selection of veterans for the emulation of a target trial evaluating the effects of newly dispensed benzodiazepine versus alternative non-benzodiazepine pharmacotherapy, among individuals consistently dispensed opioid pharmacotherapy. NOTE: No cell sizes of 10 or less are included in the reported result.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Study 3 Eligibility Exclusion

The study had an exclusion assessment window of 365 days before the index date. VHA veterans who received hospice or palliative care or had a cancer diagnosis (except non-melanoma skin cancers) were excluded. International Classification of Disease (ICD) diagnosis codes were used to identify conditions (see Appendix I for list of codes). Individuals receiving palliative care and/or in hospice were excluded given that having a terminal illness (and thus being eligible for these services) is related to both death and more permissive use of opioid pharmacotherapy and thus is a confounder in the relationship between opioid pharmacotherapy and death. In addition, individuals with cancer have an increased risk of mortality and often receive an opioid pharmacotherapy to manage cancer-related pain. Decisions regarding opioid initiation, co-prescribing, and dosage increases may differ for cancer compared to non-cancer pain; policies and practices for opioid prescribing is (generally) more permissive for individuals with cancer (VA/DoD, 2022, 2003, 2017, and 2010; Dowell et al., 2016). Furthermore, study exclusion criteria are in line with published studies examining opioid pharmacotherapy, which excluded individuals with cancer (Song et al., 2022; Coyle et al., 2018; Berna et al., 2015; Turner et al., 2015; Gomes et al., 2011; Dunn et al., 2010). As a result, having cancer may be a confounder between treatment regimen and mortality; therefore, individuals with cancer, other than non-melanoma skin cancer, were excluded.

To ensure that individuals receiving medications for opioid use disorder (MOUD) treatment were excluded from the study, the committee excluded any individuals who had received ≥1 dispensed MOUD formulation of levo-alpha acetyl methadol (LAAM), methadone, buprenorphine, or naltrexone in the 90-day pre-index period. In study 3, veterans with all qualifying episodes[8] beginning on or after October 1, 2019, were excluded to ensure that each veteran included in the study had the potential for a complete 3-month follow-up period.

The causal question for this study focuses on the effect of individuals newly dispensed benzodiazepine versus alternative non-benzodiazepine pharmacotherapy among veterans who were consistently dispensed opioid pharmacotherapy, regardless of the reason. The study did not exclude (a) veterans prescribed opioid pharmacotherapy who have an opioid use disorder (OUD) during follow-up or (b) individuals with surgery or acute painful injury within the 90 days before the index date. The committee agreed that OUD diagnosis alone is not an absolute contraindication for opioid prescribing: the OUD diagnosis may not be recent, and individuals may not actively be receiving treatment during the time of the study. In addition, OUD was not considered a covariate by the committee because it is within the causal pathway of interest. Given these reasons, the committee did not exclude individuals with an OUD diagnosis. The committee aimed to capture all opioid pharmacotherapy exposure (except cancer-related and end-of-life pain, given the increased likelihood of mortality) (see Chapter 3 for further rationale).

Study 3 excluded veterans who were dispensed both benzodiazepine and non-benzodiazepine pharmacotherapy during the same episode, which is consistent with the statement of task's focus on comparing the two ("3. The effect of co-prescribing a benzodiazepine among patients currently receiving long-term opioids, relative to alternative treatments for anxiety and other indications for benzodiazepines"). See Figure 6-2 for the selection process of veterans for the study.

Study 3 Treatment Strategies

Drawing from this study population of eligible VHA veterans, this study considers the initiation of two mutually exclusive, clinically realistic treatment strategies:

- Of those veterans consistently dispensed opioid pharmacotherapy,
  - Treatment group: newly dispensed benzodiazepine pharmacotherapy
  - Comparator group: newly dispensed alternative non-benzodiazepine pharmacotherapy.

Table 6-2 shows the list of eligible benzodiazepine pharmacotherapy and alternative non-benzodiazepine pharmacotherapy.

[8] All veteran episodes (regardless of treatment assignment).

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 6-2 Pharmacotherapies of Interest in Study 3

Drug Class	Study 3
Opioid Full Agonist[1]	
Benzhydrocodone	Population of interest
Codeine	Population of interest
Dihydrocodeine	Population of interest
Fentanyl	Population of interest
Hydrocodone	Population of interest
Hydromorphone	Population of interest
LAAM[2] (non-liquid; for pain)	Population of interest
LAAM (non-liquid; MOUD[3])	• Included in baseline exclusion criteria • Not censored during follow-up
Levomethadyl	Population of interest
Levorphanol	Population of interest
Meperidine (oral)	Population of interest
Methadone (non-liquid/non-diskette) (for pain)	Population of interest
Methadone (non-liquid/non-diskette) (MOUD)	• Included in baseline exclusion criteria • Not censored during follow-up
Morphine	Population of interest
Oxycodone	Population of interest
Oxymorphone	Population of interest
Propoxyphene	Population of interest
Sufentanil (sublingual)	Population of interest
Tramadol	Population of interest
Opioid Atypical	
Buprenorphine (MOUD)	• Included in baseline exclusion criteria • Not censored during follow-up
Buprenorphine (for pain)	• Included in baseline exclusion criteria • Not censored during follow-up
Butorphanol	Population of interest
Tapentadol	Population of interest
Opioid Antagonist	
Naltrexone	• Included in baseline exclusion criteria • Not censored during follow-up
Benzodiazepine	
Alprazolam	Benzodiazepine pharmacotherapy (treatment)
Bromazepam	Benzodiazepine pharmacotherapy (treatment)
Chlordiazepoxide	Benzodiazepine pharmacotherapy (treatment)
Clobazam	Benzodiazepine pharmacotherapy (treatment)

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 6-2 Continued

Drug Class	Study 3
Clonazepam	Benzodiazepine pharmacotherapy (treatment)
Clorazepate	Benzodiazepine pharmacotherapy (treatment)
Diazepam	Benzodiazepine pharmacotherapy (treatment)
Estazolam	Benzodiazepine pharmacotherapy (treatment)
Flurazepam	Benzodiazepine pharmacotherapy (treatment)
Halazepam	Benzodiazepine pharmacotherapy (treatment)
Lorazepam	Benzodiazepine pharmacotherapy (treatment)
Oxazepam	Benzodiazepine pharmacotherapy (treatment)
Prazepam	Benzodiazepine pharmacotherapy (treatment)
Quazepam	Benzodiazepine pharmacotherapy (treatment)
Remimazolam	Benzodiazepine pharmacotherapy (treatment)
Temazepam	Benzodiazepine pharmacotherapy (treatment)
Triazolam	Benzodiazepine pharmacotherapy (treatment)
Anti-Convulsant	
Carbamazepine	Confounder
Oxcarbazepine	Confounder
Topiramate	Confounder
Antidepressants	
Amitriptyline	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Amoxapine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Bupropion (Tab)	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Citalopram	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Clomipramine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Desipramine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Desvenlafaxine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Doxepin	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Duloxetine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Escitalopram	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 6-2 Continued

Drug Class	Study 3
Esketamine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Fluoxetine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Fluvoxamine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Impramine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Isocarboxazid	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Levomilnacipran	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Milnacipran	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Mirtazapine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Nefazodone	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Nortriptyline	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Paroxetine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Phenelzine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Protriptyline	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Selegiline	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Sertraline	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Tranylcypromine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Trazodone	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 6-2 Continued

Drug Class	Study 3
Trimipramine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Venlafaxine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Vilazodone	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Viloxazine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Vortioxetine	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Antihistamine	
Hydroxyzine	Confounder
Anxiolytic	
Buspirone	Confounder
Gabapentinoids	
Gabapentin	Not included in study
Pregabalin	Not included in study
Insomnia	
Eszopiclone	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Ramelteon	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Suvorexant	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Zaleplon	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Zolpidem	Alternative non-benzodiazepine pharmacotherapy (benzodiazepine comparator)
Migraine	
Almotriptan	Confounder
Aspirin w/ caffeine	Confounder
Eletriptan	Confounder
Fioricet	Confounder
Fioridals	Confounder
Fioridan	Confounder
Frovatriptan	Confounder

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 6-2 Continued

Drug Class	Study 3
Naratriptan	Confounder
Rizatriptan	Confounder
Sumatriptan	Confounder
Sumatriptan + Naproxen	Confounder
ZOLMitriptan	Confounder
Muscle Relaxers	
Baclofen	Not included in study
Carisoprodol	Not included in study
Chlorzoxazone	Not included in study
Cyclobenzaprine	Not included in study
Dantrolene	Not included in study
Metaxalone	Not included in study
Methocarbamol	Not included in study
Orphenadrine	Not included in study
Tizanidine	Not included in study
Other Non-Opioid Analgesic	
Acetaminophen	Confounder
Non-Steroidal Anti-Inflammatory Drug	
Aspirin (>=400mg)	Not included in study
Celecoxib	Not included in study
Diclofenac (pill)	Not included in study
Diflunisal	Not included in study
Etodolac	Not included in study
Fenoprofen	Not included in study
Flurbiprofen	Not included in study
Ibuprofen	Not included in study
Indomethacin	Not included in study
Ketoprofem	Not included in study
Ketorolac	Not included in study
Meclofenamate	Not included in study
Meloxicam	Not included in study
Nabumetone	Not included in study
Naproxen	Not included in study
Oxaprozin	Not included in study
Phenylbutazone	Not included in study
Piroxicam	Not included in study
Salsalate	Not included in study
Sulindac	Not included in study
Tolmetin	Not included in study

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 6-2 Continued

Drug Class	Study 3
Serotonin Norepinephrine Reuptake Inhibitors	
Desvenlafaxine	Benzodiazepine comparator (non-benzodiazepine alternative)
Venlafaxine	Benzodiazepine comparator (non-benzodiazepine alternative)
Tetracyclic Anti-Depressant	
Mirtazapine	Benzodiazepine comparator (alternative non-benzodiazepine)

[1] There are two types of opioids: full agonist and partial opioid agonist. Full opioid agonists fully activate the mu receptors in the brain, enabling the opioid to have "full" effect, such as codeine, oxycodone, and fentanyl. Partial opioid agonists also activate mu receptors in the brain but to a lesser degree, such as butorphanol or tapentadol.

[2] LAAM: levo-alpha acetyl methadol.

[3] MOUD: medications for opioid use disorder.

Study 3 Treatment Assignment

In the hypothetical target trial, eligible individuals would be randomly assigned by clinical researchers to a treatment strategy with their consent and followed; individuals would be aware of their treatment assignment. The emulated target trial (study 3), based in retrospective observational data, treatment assignments were based on the observed prescription drug events (claims) from Medicare Part D or dispensed pharmacotherapy from the VHA electronic health records (EHRs). Thus, the analyses considered prescription dispensing records to assign individuals to a treatment strategy, unlike in the hypothetical target trial for which researchers would determine the treatment assignment, which could be different from what medications[9] ultimately were dispensed. It is also important to distinguish the measurability of prescription dispensing data from the measurability of that which is ingested by the individual. A dispensed prescription does not necessarily mean that the medication was consumed, since these medications are commonly prescribed to be taken "as needed." For this study, a measure of individuals ingesting the medication was not available in the dataset analyzed; the committee used pharmacy dispensing data as a proxy for medications ingested by the individual. After the first dispensed eligible pharmacotherapy, 30-day pharmacotherapy episode interval was created for eligible veterans. All episodes per veteran were selected for inclusion.

Selection of Pharmacotherapies of Interest

In study 3, the committee defined initiation as receiving ≥1 tablet of either a benzodiazepine pharmacotherapy (treatment group) or alternative non-benzodiazepine pharmacotherapy (comparator group); however, in sensitivity analyses, the committee estimated the impact of receiving ≥5 tablets.

Benzodiazepine pharmacotherapy included in the analysis were those available for prescribing in VHA during the study period (2007–2019). Alternative non-benzodiazepine pharmacotherapy for the comparator group were empirically selected through a multistep approach. First, the most frequent mental health conditions among VHA individuals with dispensed benzodiazepine pharmacotherapy were identified using VA CDW EHR data: adjustment disorders, mood disorders, and anxiety. Second, the drug class most prevalent (based on VA drug class) in individuals with these diagnoses was identified: antidepressants. In addition, based on committee clinical expertise, CPGs, and existing literature, benzodiazepine pharmacotherapies are also used to treat sleep disorders, such as insomnia (Chun et al., 2021; VA/DoD, 2019; Sateia et al., 2017; Lie et al., 2015; Shepardson et al., 2014; Wilson and Nutt, 2007). Through this approach, alternative non-benzodiazepine pharmacotherapy (comparator)

[9] The committee uses the term "pharmacotherapy" throughout the report instead of "medications," "prescriptions," or "treatment," especially when referencing the committee's analyses and results.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

included SNRIs, TeCAs, and anxiolytics pharmacotherapies (included in the VHA drug class of antidepressants) and insomnia pharmacotherapies.

Study 3 Outcomes

The outcomes outlined in the statement of task are all-cause mortality and suicide mortality, which were identified through linked data from the NDI. The committee determined all-cause mortality as the primary outcome and suicide mortality as the secondary outcome. Suicide mortality is identified by the ICD-10 death codes X60-X84 (intentional self-harm), U03 (intentional self-harm (suicide)), and Y87.0 (sequelae of intentional self-harm) (Hirsch et al., 2016; CDC, 2002).

Study 3 Causal Contrast: Intent-to-Treat Effect

Adhering to the statement of task and the causal question, this analysis focused on the intent-to-treat (ITT) effect, which corresponds to the effect of being assigned to a treatment strategy (e.g., initiating benzodiazepine pharmacotherapy versus alternative non-benzodiazepine pharmacotherapy) at baseline, irrespective of subsequent cross-over or treatment discontinuation during follow-up. Treatment "adherence" is not an issue in this study, as the committee is only interested in the initiation of a pharmacotherapy, defined as a single, newly dispensed dose.

In ITT, only baseline weights were created. For ITT analysis, the inverse probability was a function of only the baseline covariates (Hernán and Robins, 2017; Robins et al., 2000). The general assumptions of this approach are the same as other target trial emulations–if there are no unmeasured confounders, no measurement error, and no model misspecification, the ITT analysis are unbiased estimates of causal effects (see chapter 3 for a detailed description of all the assumptions associated with this approach).

Study 3 Start and End of Follow-Up

In this study, the start date, or the index date, is when the veteran was first dispensed the qualifying ≥1 tablet supply of the benzodiazepine or alternative non-benzodiazepine pharmacotherapy and all baseline eligibility criteria were met. To facilitate computation, the index date was transformed into an index month, as the analyses were conducted using aggregated monthly data. Based on the study design that considered a 12-month pre-index period and a 3-month follow-up period, January 1, 2007, was the first eligible index date and October 1, 2019, was the last eligible index date. The committee utilized all available follow-up data (through the end of 2019) with prespecified landmark analysis at 3 months.

The committee selected a 3-month follow-up to estimate the acute effect of concomitantly dispensed opioid and benzodiazepine pharmacotherapy on mortality. For ITT, eligible individuals are followed from the time of treatment initiation (baseline) until death (or death due other causes, in analyses of suicide mortality) or the administrative end of follow-up (3 months), whichever happens first. All episodes per eligible veteran were selected for inclusion.

Study 3 Design

The study design was an active-comparator, new-user (Lund et al., 2015; Ray, 2003), retrospective cohort target trial emulation study (Hernán and Robins, 2016). The emulated trial using observational data was conducted to estimate the relative effect of being newly dispensed benzodiazepine pharmacotherapy versus alternative non-benzodiazepine pharmacotherapy on mortality for a follow-up period of 3 months.

Study 3 Covariates

To strengthen causal inferences, the committee controlled for many covariates to adjust for baseline confounding and achieve balance between the treatment and comparator groups (see chapter 3 for more details):

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- Sociodemographics,
- Health conditions and behaviors,
- Supplemental health insurance to VHA coverage,
- Health care utilization,
- Specific pharmacotherapies,
- Facility,
- Facility-level characteristic, and
- Calendar month of eligible dispensed pharmacotherapy.

Additional covariates include month and the interaction of state and year as fixed effects. Baseline covariates included demographic characteristics (e.g., age, sex, race/ethnicity, marital status, disability status), supplemental insurance to the VHA coverage (e.g., Medicare, TRICARE, or private insurance), housing security (e.g., history of homelessness status), physical and mental health conditions/disorders (e.g., acute painful injury, anxiety, chronic obstructive pulmonary disease, cardiovascular disease, substance use disorders, diabetes), military status (e.g., service era, military branch, combat service), body mass index, health care utilization in prior year (e.g., VHA outpatient visits, inpatient hospital admissions, nursing home stay), VHA facility-level characteristic (e.g., urbanicity), and specific pharmacotherapies that the committee considered as potential confounders (such as migraine medications; see Table 3-4 and Table 6-2 for the detailed list). The committee evaluated candidate variables readily available in the study clinical and administrative databases. See Appendix I for health conditions and corresponding ICD codes.

The studies did not require participants to have a chronic pain diagnosis in the primary analysis. Studies have shown that individuals identified with chronic pain did not have a pain diagnosis or pain was underreported in electronic medical records compared to pain reported in a patient-based survey (Frank et al., 2019; Goulet et al., 2016) The committee controlled for a number of baseline confounders in this study. Average pain intensity score was measured solely at baseline. Given the insomnia pharmacotherapy was included in the comparator group, additional specific sleep disorders (circadian rhythm sleep disorders; hypersomnia; isolated symptoms, apparently normal variants, and unresolved issues; other psychiatric/behavioral disorders frequently encountered in the differential diagnosis of sleep disorders; other sleep disorders; parasomnia; sleep disorders associated with conditions classifiable elsewhere; and sleep-related movement disorders) were included as covariates.

Lastly, based on a priori hypotheses that effects may vary by specific individual subgroups, the committee identified a subset of variables to be evaluated for effect modification (see the "Subgroup Analyses" section) (Suda et al., 2023; Gellad et al., 2018).

Accounting for Secular Trends and Variation by Facility

Facility and calendar time (12 months) were captured as fixed effects to capture facility-specific variation (e.g., clustering of individuals within a facility, geographic variation by facility), and reflect changes over time (e.g., variation in behaviors (health care seeking, prescribing)) and prevalence of conditions during a year. The committee also included the interaction term (i.e., product term) between state and year to capture unmeasured variation over time and by states, such as when state or facility policies related to opioid prescription were implemented (e.g., when states began to participate in the Prescription Drug Monitoring Program) or secular trends in state-level policies and intensities during the opioid epidemic.

Statistical Analysis

The causal effect of study 3 is the ITT effect. In study 3, an unadjusted and adjusted pooled logistic regression model was used to estimate the death rates (per 100,000 person-years) as a measure of absolute risk and HRs for all-cause mortality and suicide mortality in the benzodiazepine pharmacotherapy group compared to the alternative non-benzodiazepine pharmacotherapy group (the reference). A Wald confidence interval (CI) was calculated for the overall HR. For the subgroup analyses, the Bonferroni correction was applied to calculate the 95 percent CIs and adjust for multiple comparisons. The survival curves for all-cause and suicide mortality over time for those newly

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dispensed benzodiazepine pharmacotherapy compared to those newly dispensed alternative non-benzodiazepine pharmacotherapy were estimated.

All analyses were conducted using SAS 9.4 and SAS Enterprise Guide. The study results do not report data if sample sizes were 10 or fewer individuals. This helps to ensure confidentiality of individuals in the study and is in line with CMS data policy and National Center for Health Statistics (NCHS) recommendations (NCHS, 2023; HHS, 2020). Furthermore, cells are marked as unreliable where sample sizes were 20 or fewer.

Accounting for Baseline Differences: Inverse Probability Treatment Weights

To account for the baseline difference between treatment and comparator groups in each target trial, analyses were weighted using inverse probability treatment weights (IPTW) for studies 1 and 3. IPTW is a method used to adjust for covariates and potential confounding in observational studies that uses a function of the propensity score (PS) of receiving treatment based on individual factors. By weighting each individual included in the analysis by the inverse of the probability of receiving the treatment or comparator treatment helps achieve balance between the treatment and comparator groups (Xu et al., 2010; Robins, 1986).

To calculate the IPTW, the committee first performed a logistic regression to calculate the PS, or the likelihood of being the treatment versus comparator group. The PS, the dependent variable, was conditioned on the aforementioned covariates. For ITT analysis, the IPTW was a function of only the baseline covariates (Robins et al., 2000). Second, the IPTW was calculated using the inverse of the PS, or 1/PS, for those newly dispensed benzodiazepine pharmacotherapy and 1/(1-PS) for those newly dispensed alternative non-benzodiazepine pharmacotherapy group for baseline treatment strategies.

To limit the influence of extreme weights on the results, the committee winsorized weights to the middle 98 percent by applying the 1st percentile weight to all observations below the 1st percentile and the 99th percentile weight to all observations above the 99th percentile (Crump et al., 2009). The distribution of the PS by treatment strategy was depicted using histograms. In addition, the balance of baseline covariates between the two groups before and after IPTW was assessed using the absolute standardized mean difference (ASMD). An ASMD of ≤0.1 between the two groups after weighting suggests reduction of potential confounding, allowing for causal inference comparisons (Austin, 2009). Missing values were handled using the missing covariate indicator methods, which assigned a missing category in the model (e.g., Hispanic ethnicity, non-Hispanic ethnicity, missing ethnicity).

Descriptive Analyses

The committee reports the distributions of baseline demographic and clinical characteristics for the overall analytic sample before and after application of the IPTW weights.

Subgroup Analyses

Subgroup analyses were conducted by age (with two categorical comparisons: 18–64 versus ≥65 and 18–34, 35–54, 55–74, ≥75), race (White, Black, Native American/Alaskan Native, Asian, Hawaiian and Pacific Islander, more than one race, and missing), ethnicity (Hispanic, and non-Hispanic), sex (male and female), time period (2007–2012 versus 2014–2019), and by payment source of dispensed prescriptions (only Medicare Part D prescription claims, only VHA prescription claims, or both during the episode). The committee selected these subgroups to examine differences given older age groups, specific racial and ethnic groups, and males have been shown to be at increased risk for mortality (Bohnert and Ilgen, 2019; Bossarte et al., 2012). Age categories used in the national annual reports on veteran suicide prevention were included in the subgroup analysis for consistency (VA, 2018).

The committee also included time period to examine changes in mortality risk. The committee selected before or after 2013, given introduction of the VHA's Opioid Safety Initiative that year. The committee stratified by payment sources of dispensed pharmacotherapy during an episode: individuals were grouped as having prescriptions dispensed from only the VHA, only Medicare Part D, or both. Payment source of dispensed pharmacotherapy is a proxy for care, access, and coordination.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Sensitivity Analyses

Sensitivity analyses were conducted to assess the robustness of the results. First, the period of follow-up for outcome measurement was extended from 3 to 12 months from the index date. Second, the number of dispensed tablets was increased from at least one to at least five, and thus the index date was redefined to the date when the individual was dispensed at least five tablets of a benzodiazepine or alternative non-benzodiazepine pharmacotherapy.

RESULTS

Among the 13,152,784 million unique veterans who received care in the VHA from 2007–2019, 637,793[10] were consistently dispensed opioid pharmacotherapy and eligible for inclusion. The mean age and standard deviation (SD) age at first visit was 60.65 years (SD: 13.74). Most study participants were male (93.67 percent), White (71.89 percent), and non-Hispanic (89.98 percent). They accounted for 1,379,093 unique veteran episodes for a mean of 2.19 (1.84) episodes per veteran and 4,103,911 veteran-months of observation for a mean follow-up time of 2.98 (SD: 0.20) months per episode. The sociodemographic and clinical characteristics of the study sample before and after weighting are presented in Table 6-3. After weighting, the maximum ASMD was less than 0.1, suggesting good covariate balance (Figure 6-5).

From 2007 through 2019, 16,913 deaths from all causes and 303 by suicide mortality occurred in this cohort. Among deaths from all causes, 4,768 occurred during an episode involving benzodiazepine pharmacotherapy (N = 123,684), resulting in an adjusted all-cause mortality rate of 7,493 deaths per 100,000 person-years of observation. Conversely, 12,145 deaths occurred during an episode involving an alternative non-benzodiazepine pharmacotherapy (N = 565,481), resulting in an adjusted all-cause mortality rate of 4,392 deaths per 100,000 person-years. The adjusted HR for all-cause mortality was 1.71 (95% CI: 1.60–1.82; unadjusted HR: 2.72 [95% CI: 2.58–2.96]). See Table 6-4 for unadjusted and IPTW adjusted all-cause and suicide mortality results.

Among the deaths from suicide, 64 occurred during a veteran episode involving newly dispensed benzodiazepine pharmacotherapy (N = 123,684), resulting in an adjusted suicide mortality rate of 117.0 suicides per 100,000 person-years of observation. Conversely, 239 suicide deaths occurred during a veteran episode involving newly dispensed alternative non-benzodiazepine pharmacotherapy (N = 565,481), resulting in an adjusted suicide mortality rate of 82.5 deaths per 100,000 person-years. The adjusted HR for suicide mortality was 1.42 (95% CI: 0.87–2.31; unadjusted HR: 1.85 [95% CI: 0.87–2.31]). Survival curves demonstrate lower survival over time in those newly dispensed benzodiazepine pharmacotherapy compared to those newly dispensed alternative non-benzodiazepine pharmacotherapy (see Figure 6-3).

The subgroup results, when available, are consistent with the overall estimates for both all-cause mortality and suicide mortality (Tables 6-5 and 6-6). This suggests that the primary results were not driven by a particular subgroup and that the risk across subgroups is similar. Consistent with both the CMS data policy and NCHS recommendations, the results in Tables 6-5 and 6-6 do not report estimates if sample sizes were fewer than 10 individuals, and estimates are marked as unreliable where sample sizes were fewer than 20.

Sensitivity Analyses

Two sensitivity analyses were run: (1) the follow-up time of the primary analysis extended to 12 months and (2) the index of exposure to benzodiazepine or alternative non-benzodiazepine pharmacotherapy increased to at least five tablets. The results were highly consistent (see Table 6-5).

The sensitivity analysis examining the effect of ≥5 tablets resulted in consistent results for all-cause mortality as the main analysis examining the effect of ≥1 tablets. Even when exposure to the treatment was more restrictive (e.g., required to have a higher number of tablets (≥5) compared at least one tablet), all-cause mortality results

[10] The total number of unique veterans in study 3 is 637,793. During the study period (2007–2019), a veteran could enter the study more than one time and contributed more than 1 episode. Thus, the number of veterans in the benzodiazepine group (N = 123,684) and alternative non-benzodiazepine comparator (N = 565,481) will not sum to 637,793.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 6-3 Among VHA Veterans Consistently Dispensed Opioid Pharmacotherapy, Baseline Characteristics of Veterans Included in the Current Analysis by Newly Dispensed Pharmacotherapy Group (Benzodiazepine Pharmacotherapy Versus Alternative Non-Benzodiazepine Pharmacotherapy) Before and After Inverse Probability Treatment Weights (IPTW) (2007–2019)

	Before Weighting			After IPTW		
Covariate	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)	ASMD[1]	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)	ASMD
Sex						
Male	94.43	93.54	0.04	93.35	93.65	0.01
Female	5.57	6.46	0.04	6.65	6.35	0.01
Missing						
Age						
18–34	2.96	4.18	0.07	4.22	4.03	0.01
35–54	16.59	23.47	0.17	22.94	22.61	0.01
55–74	57.39	60.30	0.06	59.59	59.93	0.01
75+	23.06	12.06	0.29	13.25	13.43	0.01
Race						
White	75.46	70.43	0.11	70.99	71.06	0.00
Black	11.23	18.19	0.20	17.39	17.32	0.00
Asian	0.17	0.24	0.01	0.23	0.23	0.00
Native American	0.83	0.94	0.01	0.96	0.92	0.00
Pacific Islander	0.73	0.68	0.01	0.70	0.69	0.00
Multiracial	0.78	0.89	0.01	0.89	0.88	0.00
Missing	10.81	8.63	0.07	8.85	8.90	0.00
Ethnicity						
Non-Hispanic	89.21	90.66	0.05	90.47	90.49	0.00
Hispanic	4.26	4.30	0.00	4.31	4.30	0.00
Missing	6.53	5.03	0.06	5.22	5.22	0.00
Marital Status						
Married	50.07	47.70	0.05	48.06	48.01	0.00
Not Married	44.53	47.29	0.06	46.98	46.94	0.00
Missing	5.39	5.01	0.02	4.97	5.06	0.00
Disability Status *(Based on VA Enrollment Priority Group)*						
Group 1	28.02	35.31	0.16	34.85	34.41	0.01
Group 2	6.66	8.15	0.06	8.00	7.96	0.00
Group 3	9.89	10.36	0.02	10.20	10.30	0.00
Group 4	2.66	1.83	0.06	1.93	1.93	0.00
Group 5	34.24	31.96	0.05	31.91	32.22	0.01
Group 6	1.77	1.45	0.03	1.46	1.49	0.00
Group 7	2.19	1.44	0.06	1.51	1.53	0.00

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 6-3 Continued

	Before Weighting			After IPTW		
Covariate	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)	ASMD[1]	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)	ASMD
Group 8	14.39	9.40	0.16	10.01	10.03	0.00
Missing	0.18	0.12	0.02	0.13	0.13	0.00
Housing Security						
History of Homelessness (yes/no)	10.96	15.56	0.14	15.18	14.98	0.01
Health Behavior						
Tobacco Use Ever (yes/no)	55.28	60.99	0.12	60.13	60.26	0.00
Health Conditions						
Physical Health Conditions						
Acute Pain Injury	14.87	17.45	0.07	17.69	17.15	0.01
AIDS/HIV	0.48	0.55	0.01	0.53	0.54	0.00
Blood Loss Anemia	1.44	1.47	0.00	1.53	1.47	0.01
Cancer (non-melanoma skin)	0.68	0.75	0.01	0.74	0.74	0.00
Cardiovascular Disease	23.51	19.29	0.10	20.08	19.85	0.01
Cerebrovascular Disease	5.41	4.66	0.03	4.94	4.77	0.01
Chronic Lung Disease	21.93	20.95	0.02	21.18	21.08	0.00
Cirrhosis	1.57	1.55	0.00	1.57	1.55	0.00
COPD[2]	5.99	6.28	0.01	6.12	6.24	0.01
Deficiency Anemia	7.14	5.97	0.05	6.20	6.13	0.00
Dementia	2.50	2.28	0.01	2.38	2.31	0.01
Diabetes	27.40	30.70	0.07	30.59	30.30	0.01
End Stage Renal Disease	1.11	0.79	0.03	0.87	0.83	0.00
Heart Disease	23.00	18.87	0.10	19.68	19.42	0.01
Hepatitis	2.78	3.32	0.03	3.23	3.25	0.00
Hemiplegia or Paraplegia	1.46	1.10	0.03	1.18	1.15	0.00
Liver Disease	3.03	3.16	0.01	3.20	3.15	0.00
Migraine	2.75	3.67	0.05	3.72	3.56	0.01
Peptic Ulcer Disease	0.86	0.78	0.01	0.81	0.79	0.00
Peripheral Vascular Disease	6.21	5.70	0.02	5.78	5.77	0.00
Pulmonary Circulation Disorders	0.38	0.45	0.01	0.43	0.44	0.00
Rheumatic Disease	57.78	59.92	0.04	60.58	59.70	0.02
Syncope	0.70	0.77	0.01	0.79	0.76	0.00
Sleep Disorders						
Apnea	5.96	8.46	0.10	8.38	8.15	0.01
Circadian Rhythm Sleep Disorders	0.04	0.06	0.01	0.06	0.05	0.00

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 6-3 Continued

	Before Weighting			After IPTW		
Covariate	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)	ASMD[1]	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)	ASMD
Hypersomnia	0.10	0.17	0.02	0.16	0.16	0.00
Insomnia	1.79	1.74	0.00	1.82	1.75	0.01
Isolated Symptoms, Apparently Normal Variants, and Unresolved Issues	5.97	5.55	0.02	5.68	5.61	0.00
Other Sleep Disorders	0.23	0.46	0.04	0.46	0.43	0.00
Parasomnia	0.09	0.07	0.01	0.07	0.08	0.00
Sleep Disorders Associated with Conditions Classifiable Elsewhere	14.76	16.95	0.06	17.08	16.68	0.01
Sleep-Related Movement Disorders	0.40	0.43	0.01	0.45	0.43	0.00
Mental Health						
Attention-Deficit/ Hyperactivity Disorder	0.23	0.23	0.00	0.24	0.23	0.00
Anxiety	7.91	6.23	0.07	6.57	6.45	0.01
Bipolar Disorder	2.28	2.12	0.01	2.32	2.14	0.01
Depression	8.65	15.96	0.22	15.54	15.05	0.01
Substance Use Disorders						
Drug Use Disorder	1.38	2.58	0.09	2.44	2.43	0.00
Opioid Use Disorder	0.85	1.06	0.02	1.09	1.03	0.01
Alcohol Use Disorder	2.67	4.23	0.09	4.09	4.03	0.00
Posttraumatic Stress Disorder	8.71	12.65	0.13	12.88	12.17	0.02
Schizophrenia and Psychosis	1.20	1.26	0.01	1.28	1.25	0.00
Suicidal Ideation	0.22	0.31	0.02	0.32	0.30	0.00
Traumatic Brain Injury	1.82	1.77	0.00	1.81	1.78	0.00
Overdose-Related Diagnoses						
Opioid Overdose Diagnosis (in last 12 months)	0.06	0.04	0.01	0.04	0.04	0.00
Current Pain Intensity Rating (in past month)						
Pain 0	11.94	10.42	0.05	10.52	10.63	0.00
Pain 1	1.95	1.60	0.03	1.65	1.65	0.00
Pain 2	2.75	2.47	0.02	2.55	2.51	0.00
Pain 3	4.26	4.25	0.00	4.32	4.26	0.00
Pain 4	4.61	4.99	0.02	5.06	4.95	0.01
Pain 5	5.32	5.94	0.03	5.98	5.87	0.00
Pain 6	4.81	5.84	0.05	5.78	5.72	0.00

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 6-3 Continued

	Before Weighting			After IPTW		
Covariate	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)	ASMD[1]	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)	ASMD
Pain 7	4.81	6.08	0.06	6.10	5.93	0.01
Pain 8	4.31	5.81	0.07	5.65	5.62	0.00
Pain 9	1.82	2.39	0.04	2.39	2.32	0.01
Pain 10	1.51	1.92	0.03	1.96	1.87	0.01
Missing	51.92	48.28	0.07	48.05	48.68	0.01
Body Mass Index						
Underweight	1.25	1.11	0.01	1.10	1.12	0.00
Normal	18.04	17.36	0.02	17.31	17.45	0.00
Overweight	28.87	30.35	0.03	30.07	30.19	0.00
Obese	37.17	44.89	0.16	44.51	43.95	0.01
Missing	14.68	6.29	0.28	7.01	7.29	0.01
Health Care Coverage						
Supplemental Health Insurance to VHA Coverage	42.89	49.99	0.14	49.45	49.11	0.01
Medicare only (ever/never)	27.85	11.24	0.43	12.85	13.28	0.01
Health Care Utilization in Past Year						
Number of VHA Outpatient Visits						
Outpatient Visits (0–4)	12.31	4.23	0.30	4.95	5.20	0.01
Outpatient Visits (4–11)	12.87	8.96	0.13	9.02	9.44	0.01
Outpatient Visits (12–21)	15.28	14.87	0.01	14.48	14.92	0.01
Outpatient Visits (22–42)	23.47	27.61	0.10	26.92	27.10	0.00
Outpatient Visits (43–67)	15.47	19.40	0.10	19.24	18.92	0.01
Outpatient Visits (68+)	20.60	24.93	0.10	25.39	24.43	0.02
Inpatient Hospital Admission	0.35	0.37	0.00	0.39	0.37	0.00
Inpatient Procedure	0.35	0.37	0.00	0.39	0.37	0.00
Inpatient Surgery	2.98	3.10	0.01	3.14	3.09	0.00
Outpatient Procedure	1.46	1.38	0.01	1.44	1.39	0.00
Nursing Home Visit (Yes/No)	0.68	0.69	0.00	0.72	0.69	0.00
Military Status						
Service Era						
Gulf War	11.63	18.87	0.20	18.35	17.96	0.01
Korean War	10.30	5.47	0.18	6.06	6.08	0.00
Peacetime, only	21.49	21.41	0.00	21.14	21.41	0.01
Vietnam	45.81	47.57	0.04	47.29	47.35	0.00

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table 6-3 Continued

	Before Weighting			After IPTW		
Covariate	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)	ASMD[1]	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)	ASMD
WWII, only	6.39	2.80	0.17	3.20	3.24	0.00
Multiple Eras	2.87	3.05	0.01	3.01	3.03	0.00
Missing	1.51	0.84	0.06	0.94	0.92	0.00
Combat Service (yes/no)						
Combat Service	13.97	15.20	0.04	15.24	15.06	0.01
Missing	8.28	8.23	0.00	8.04	8.23	0.01
Military Sexual Trauma (yes/no)						
Military Sexual Trauma	4.26	5.03	0.04	5.11	4.94	0.01
Missing	2.16	1.58	0.04	1.70	1.65	0.00
Military Branch						
Air Force	11.11	10.89	0.01	10.98	10.92	0.00
Army	46.45	51.35	0.10	50.57	50.73	0.00
Marine	7.40	8.81	0.05	8.64	8.63	0.00
Navy	16.47	16.24	0.01	16.32	16.27	0.00
Missing	18.57	12.72	0.16	13.48	13.46	0.00
Prescription Information *(Yes/No)*						
Anticonvulsant	1.93	2.28	0.03	2.26	2.24	0.00
Antihistamine	3.06	5.03	0.10	4.78	4.79	0.00
Anxiolytic	1.59	2.42	0.06	2.24	2.31	0.01
Buprenorphine (for Pain)	0.12	0.24	0.03	0.42	0.22	0.04
Migraine pharmacotherapy	3.14	4.04	0.05	3.94	3.93	0.00
Acetaminophen	59.62	57.10	0.05	57.54	57.41	0.00
Facility Urbanicity						
Non-Core	26.48	35.90	0.20	34.41	34.71	0.01
Micropolitan	6.24	6.40	0.01	6.48	6.38	0.00
Small Metro	20.28	25.79	0.13	25.07	25.11	0.00
Medium Metro	5.89	6.80	0.04	6.56	6.69	0.01
Large Fringe Metro	4.89	6.81	0.08	6.41	6.57	0.01
Large Central Metro	0.21	0.18	0.01	0.18	0.19	0.00
Missing	36.01	18.12	0.41	20.88	20.36	0.01

[1] Absolute standardized mean difference.
[2] Chronic obstructive pulmonary disease.
NOTE: No cell sizes of 10 or less are included in the reported results.

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Table 6-4 Among VHA Veterans Consistently Dispensed Opioid Pharmacotherapy, All-Cause Mortality and Suicide Mortality Rates and Hazard Ratios in those Newly Dispensed Benzodiazepine Pharmacotherapy Versus Alternative Non-Benzodiazepine Pharmacotherapy at 3 Months (2007–2019) (veterans: $N = 637{,}793$, veteran episodes: $n = 1{,}379{,}093$)

	Unweighted Results					IPTW Results				
	Mortality Rate (Deaths per 100,000 person-years)		Hazard Ratio	Lower (95% CI)	Upper (95% CI)	Mortality Rate (Deaths per 100,000 person-years)		Hazard Ratio	Lower (95% CI)	Upper (95% CI)
Outcome	Benzodiazepine Pharmacotherapy ($n = 174{,}623$)*	Alternative Non-Benzodiazepine Pharmacotherapy ($n = 1{,}204{,}470$)**				Benzodiazepine Pharmacotherapy ($n = 174{,}623$)	Alternative Non-Benzodiazepine Pharmacotherapy ($n = 1{,}204{,}470$)			
All-cause mortality	11,038.00	4,065.00	2.72	2.58	2.86	7,493.00	4,392.00	1.71	1.60	1.82
Suicide mortality	148.20	80.00	1.85	1.20	2.86	117.00	82.50	1.42	0.87	2.31

*$N = 123{,}684$; **$N = 565{,}481$.

NOTES: CI = confidence interval; N = unique veterans; n = veteran episodes. No cell sizes of 10 or less are included in the reported results.

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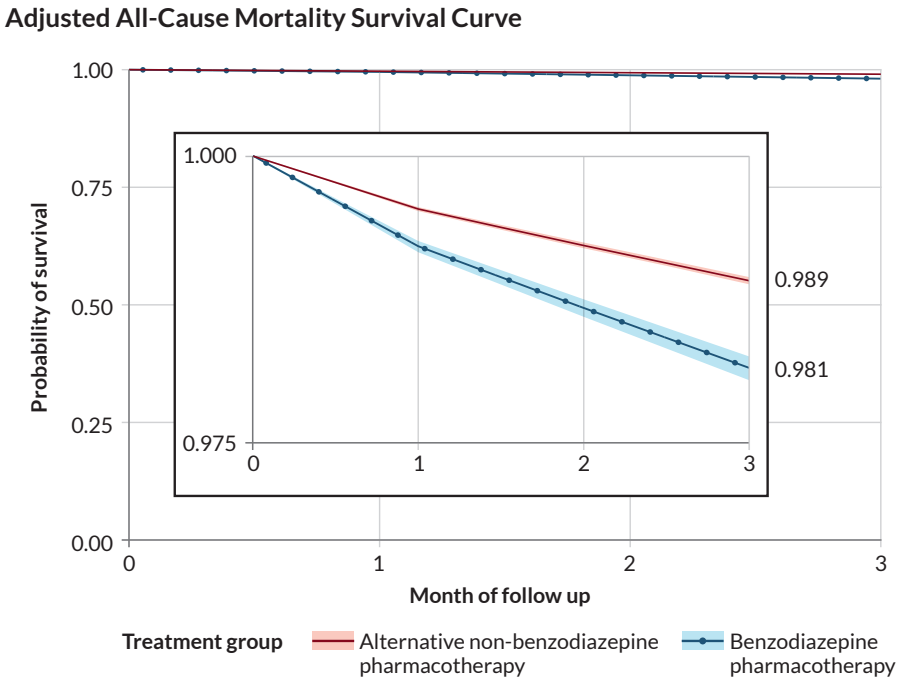

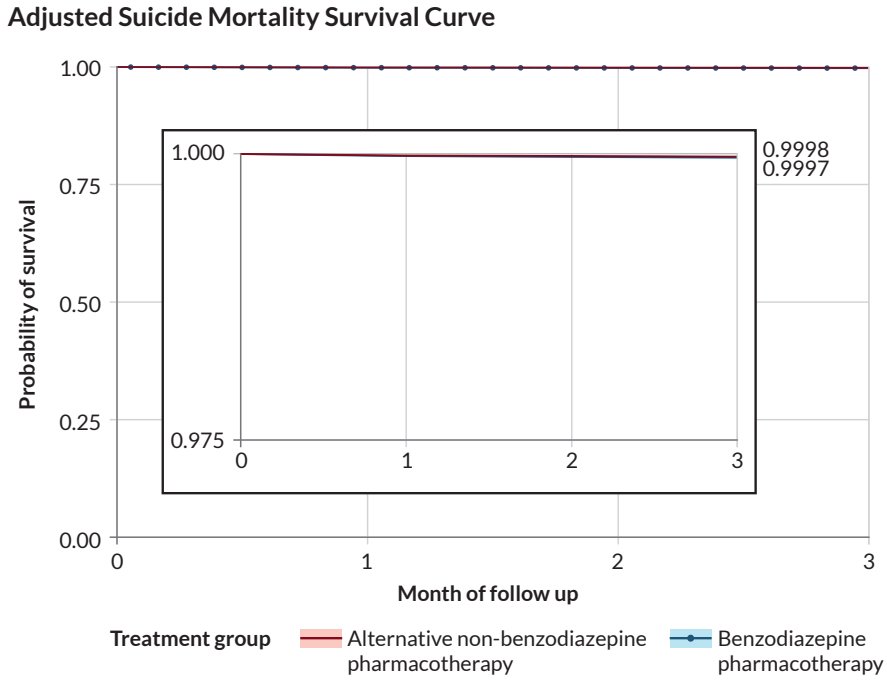

FIGURE 6-3 Among VHA veterans consistently dispensed opioid pharmacotherapy, adjusted survival curves for all-cause mortality (top panel) and suicide mortality (bottom panel) among those newly dispensed benzodiazepine pharmacotherapy versus non-benzodiazepine pharmacotherapy at 3 months (2007–2019) (veterans: $N = 637{,}793$, veteran episodes: $n = 1{,}379{,}093$). NOTES: No cells are reported representing 10 or fewer veterans. In the insert figure, the y-range is compressed.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 6-5 Among VHA Veterans Consistently Dispensed Opioid Pharmacotherapy, Inverse Probability Treatment Weighting Death Rates and Hazard Ratios for the All-Cause Mortality and Suicide Mortality Overall at 3 Months with Any Amount of Benzodiazepine and Sensitivity Analysis Outcomes (Those Dispensed at Least Five Tablets of Benzodiazepines Versus Alternative Non-Benzodiazepine Over 3 Months or Those Dispensed at Least One Tablet With an Extended Follow-Up (12 months) (2007–2019)

	Adjusted				
	Benzodiazepine (Treatment)	**Alternative Non-Benzodiazepine (Comparator)**	**Hazard ratio**	**Lower**	**Upper**
Sensitivity Analysis	*(Rate per 100,000 person-years)*			95% CI	95% CI
All-Cause Mortality at 3 months (Overall)	7,493	4,392	1.71	1.60	1.82
≥5 pills of pharmacotherapy	7,918	4,389	1.80	1.69	1.93
Extend Follow-up to 12 months	10,072	7,671	1.31	1.28	1.35
Suicide Mortality (Overall)	117	83	1.42	0.87	2.31
≥5 pills of pharmacotherapy	135	82	1.64	1.00	2.69
Extend Follow-up to 12 months	170	116	1.46	1.19	1.80

NOTES: No cells are reported representing 10 or fewer veterans. Overall indicates: ≥1 pills and 3-month follow-up.

were consistent, though less precise with wider confidence intervals due to a smaller sample size. Similarly, the suicide mortality results when analysis adjusted to ≥5 tablets was elevated.

When the analysis follow-up period was extended to 12 months, the all-cause mortality result was consistent but attenuated to 1.31 (95% CI: 1.28–1.35). The 12-month follow-up analysis for suicide mortality was consistent with the primary result at 3 months; (aHR: 1.46; 95% CI: 1.19–1.80).

See supplementary Tables 6-6, 6-7, and 6-8 and Figures 6-4, 6-5, 6-6, 6-7, and 6-8 and for further details.

DISCUSSION

Study 3 examined the effect on all-cause mortality and suicide mortality of newly dispensed benzodiazepine pharmacotherapy on veterans receiving care at the VHA. The study was conducted in response to the statement of task to examine (c) the effect of co-prescribing a benzodiazepine among individuals already receiving opioids, relative to alternative treatments for anxiety and other indications for benzodiazepines.

All-Cause Mortality and Suicide Mortality

The study findings are consistent with the literature on the risks of co-prescribing benzodiazepines with opioids. Co-prescribing is known to contribute to falls, injuries, and overdose as well as contribute to the suppression of respiratory drive.

Although benzodiazepine pharmacotherapy is effective in the treatment of several conditions, it is associated with risk of misuse, dependence, overdose, and mortality. For example, Maust and colleagues (2019) reported that of the 30.6 million U.S. adults reporting benzodiazepine use in the past year, with 17.2 percent of use reported as misuse.[11] Long-term benzodiazepine use increases the risk for benzodiazepine use disorder and dependence, which

[11] Misuse in Maust and colleagues (2019) referenced the pre-2015 NSDUH definition of "nonmedical use," but the 2015 definition was revised to include "in any way a doctor did not direct."

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is known to lead to harmful psychological and physical effects (Hirschtritt et al., 2021; Schweizer and Rickels, 1998). Furthermore, withdrawal from benzodiazepine use can result in severe, even life-threatening, symptoms (Edinoff et al., 2021; Ashton, 2005; Schweizer and Rickels, 1998; Pétursson, 1994; Ashton, 1991). Approximately 40 percent of individuals who abruptly ended long-term use (6 months or more) of long-acting benzodiazepines reported moderate to severe withdrawal (Hood et al., 2012; Murphy and Tyrer, 1988). Benzodiazepines can interact with alcohol and other psychoactive medications, especially those that act as central nervous system depressants, increasing the risk of adverse effects (Rawy et al., 2024; Hayes et al., 2020; Day, 2014; Neutel and Patten, 1997).

The committee evaluated the results based on several Bradford Hill criteria: biological plausibility, consistency of the association, time sequence, specificity, strength of the association, study design, quantitative strength, and dose response (Hill, 1965).

Biologically, both opioid and benzodiazepine pharmacotherapies are demonstrated to lead to respiratory depression, hypoxia, hypercapnia, which can cause cardiorespiratory arrest and eventually death. The study design follows individuals from their start date or entry into the study, based on their treatment strategies, and observes them over 3 months until when the outcome of interest, all-cause mortality or suicide mortality, occurs. Further, the results found were consistent across subgroups and sensitivity analyses. When the follow-up period was extended from 3 to 12 months, the aHR for all-cause mortality was attenuated. The committee's findings are consistent with studies of different design and time period, such as by Xu and colleagues (2020), who found similar results when comparing groups receiving both benzodiazepines and opioids versus those who received neither (aHR: 2.04; 95% CI: 1.65–2.52). Further, Gaither and colleagues (2016) found that concomitant opioid and benzodiazepine prescribing contributed to an increased risk in a propensity-matched sample (aHR: 1.39; 95% CI: 1.12–1.66). Weisberg and colleagues (2015) found that those receiving both long-term opioid and benzodiazepine prescriptions had a higher risk for all-cause mortality (aHR: 1.51; 95% CI 1.22–1.87) compared to those who received neither pharmacotherapy.

The strength of association reflects quantitative strength, study design, and dose response. The study design emulates a randomized trial using observational data and reduces the confounders and biases inherent in observational studies. Increasing exposure from at least one tablet to at least five tablets demonstrated similar results for all-cause mortality and suicide mortality at 3 months, suggesting minimal dose response within a narrow range of exposure. As for the study design, the committee applied the target trial emulation framework, reflecting current best practices in the causal inference methodology field when using observational data.

These findings are consistent with concerns in guidelines that indicate avoidance of concurrent use of opioid and benzodiazepine pharmacotherapy (VA/DoD, 2017, 2022; Dowell et al 2016). In addition, guidelines recommending against concurrent opioid and benzodiazepine pharmacotherapy prescribing are complemented by the decrease of co-prescribing in recent years—from 31.2 per 100 persons in 2017 to 25.8 per 100 persons in 2021.[12] It is important to note that the committee's interpretation of the results is not intended to influence restriction for any medication nor is not to be viewed as an absolute contraindication for the clinical use of benzodiazepines with opioids.

Limitations

The committee attempted to enable sufficient control for confounders; however, there remains a risk of confounding by indication (e.g., comparator group is not a sufficient comparator). Furthermore, the committee is unable to reasonably control for clinical decision making and confounding by indication. This includes the acknowledgment of risk, veteran informed consent, and the decision to use benzodiazepines anyway, perhaps especially in at-risk individuals.

Additionally, there remains an underlying acknowledgment of the reliability of medical examiner attributions regarding intentional versus non-intentional suicide. There is also the uncontrollable factor of the contribution of specific pharmacotherapies and substances in the context of multiple agents being present at the time of death.

[12] Dr. Christopher Jones. Presentation to the committee on March 9, 2023. Trends in Opioid and Benzodiazepine Use, Misuse, and Overdose.

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The committee notes the sample does not include VHA veterans who are receiving care in the private sector other than Medicare (e.g., commercial insurance or Medicaid) and the limitation this poses to the generalizability of the results.

See Chapter 3 for additional study 3 limitations.

FINDINGS

The committee was tasked with quantifying the effects of opioid and benzodiazepine prescribing on the risk of death among veterans who received care from the VHA between 2007–2019. Study 3 effectively addresses the objective outlined in part (c) the effect of co-prescribing a benzodiazepine among patients already receiving opioids, relative to alternative treatments for anxiety and other indications for benzodiazepines.

Finding 3-1. Among veterans consistently dispensed opioid pharmacotherapy, the 3-month risk for all-cause mortality was 7,493 deaths per 100,000 person-years for those newly dispensed benzodiazepine pharmacotherapy and 4,392 per 100,000 person-years for those newly dispensed alternative non-benzodiazepine pharmacotherapy (aHR: 1.71, 95% CI: 1.60–1.82).[13]

Finding 3-2. Among veterans consistently dispensed opioid pharmacotherapy, the 3-month risk for suicide mortality was 117 deaths per 100,000 person-years for those newly dispensed benzodiazepine pharmacotherapy and 83 deaths per 100,000 person-years for those newly dispensed alternative non-benzodiazepine pharmacotherapy (aHR: 1.42, 95% CI: 0.87– 2.31).[14]

CONCLUSIONS

The committee evaluated the effect of newly dispensed benzodiazepine pharmacotherapy on all-cause mortality and suicide mortality. The studies focused on effects of co-prescribing of opioids and benzodiazepine pharmacotherapies. The committee employed the TTE framework to reduce biases, such as due to immortal time, and confounding. In addition, the committee leveraged the large observational datasets (e.g., health care, clinical, and administrative data) available within the VA and VHA, supplemented by CMS data, and the NDI for mortality data. Based on the study findings, the committee makes the following conclusions for veterans who received care from the VHA between 2007–2019:

Conclusion 2. The committee concludes that there is an increased risk of all-cause mortality among veterans co-prescribed opioid and benzodiazepine pharmacotherapies compared to those co-prescribed opioid and alternative non-benzodiazepine pharmacotherapies.

Conclusion 7. The committee concludes that there is some evidence of a higher risk of suicide mortality among veterans co-prescribed opioid and benzodiazepine pharmacotherapy, although the estimate is imprecise at 3 months.

[13] Alternative non-benzodiazepine pharmacotherapy can be used to treat conditions treated by benzodiazepines, such as anxiety.
[14] Alternative non-benzodiazepine pharmacotherapy can be used to treat conditions treated by benzodiazepines, such as anxiety.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

ANNEX: SUPPLEMENTARY FIGURES AND TABLES

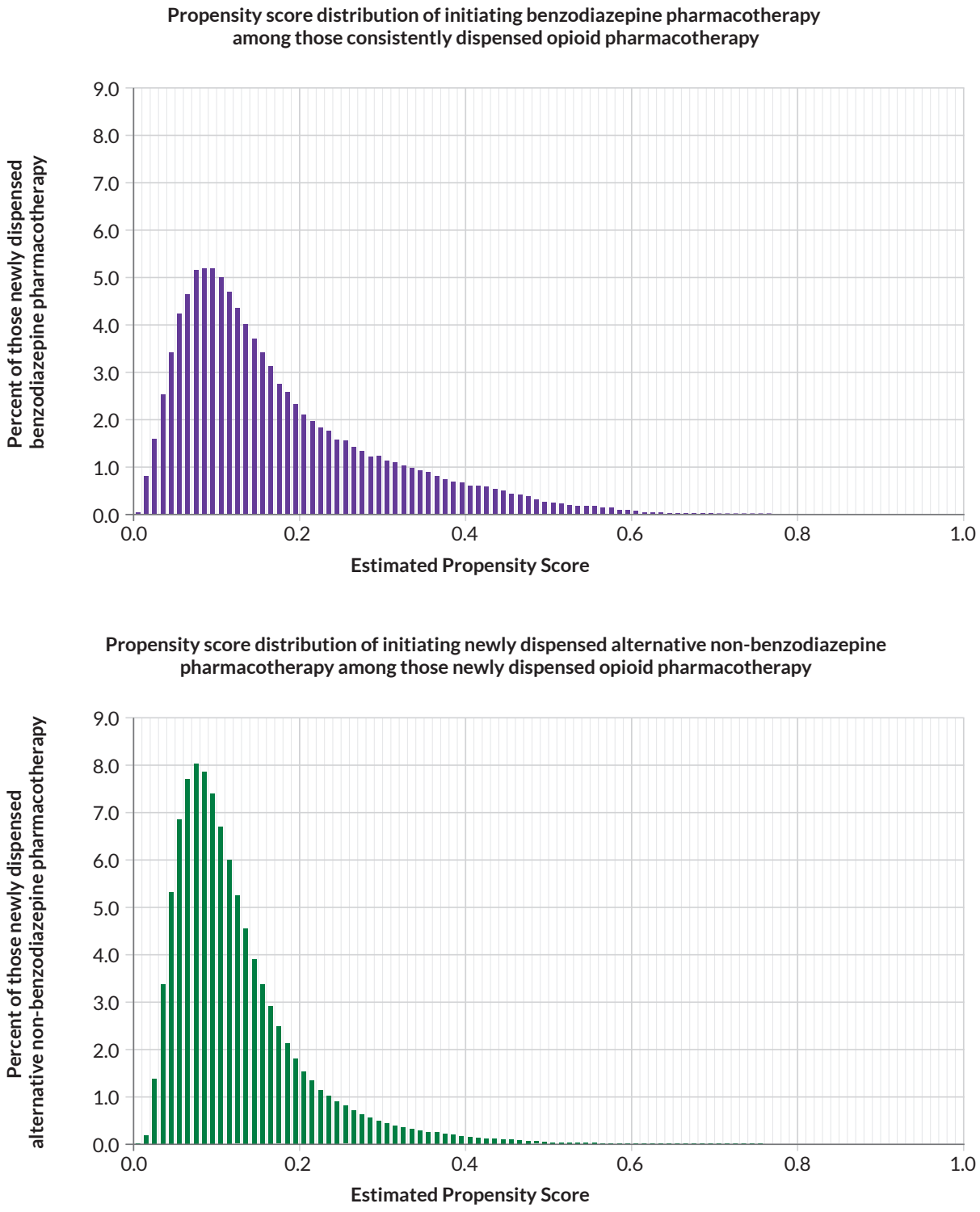

FIGURE 6-4 Among VHA veterans consistently dispensed opioid pharmacotherapy, distribution of the propensity scores for those newly dispensed benzodiazepine pharmacotherapy (top panel) versus those newly dispensed alternative non-benzodiazepine pharmacotherapy (bottom panel).
NOTE: No cells are reported representing 10 or fewer veterans.

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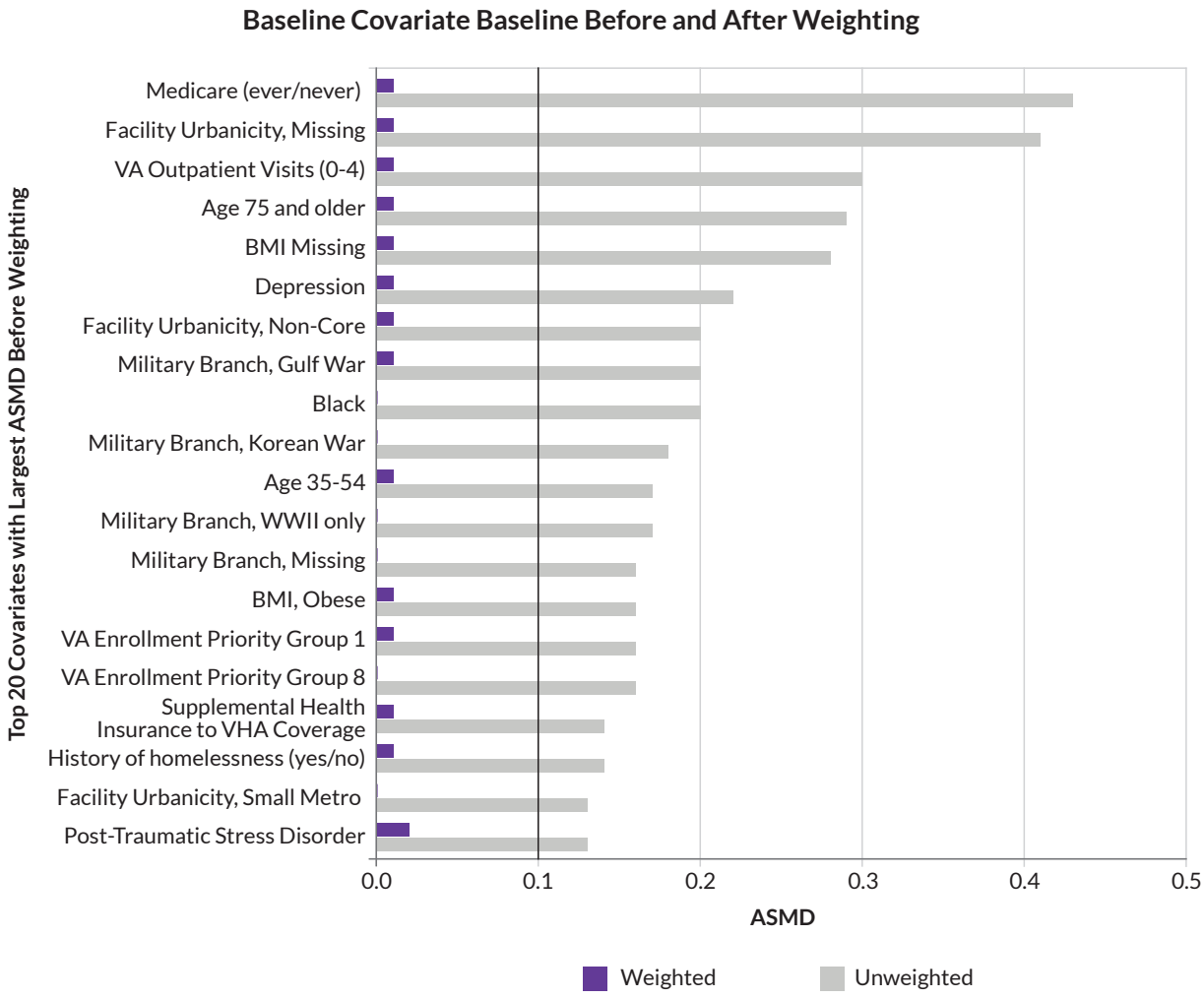

FIGURE 6-5 Among VHA veterans consistently dispensed opioid pharmacotherapy, baseline covariate balance between those newly dispensed benzodiazepine pharmacotherapy versus those newly dispensed alternative non-benzodiazepine pharmacotherapy before and after inverse probability treatment weights (IPTW).
NOTES: No cells are reported representing 10 or fewer veterans; only the 20 covariates with the greatest magnitude of change presented in figure. ASMD = adjusted standardized mean difference; BMI = Body Mass Index.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 6-6 Among VHA Veterans Consistently Dispensed Opioid Pharmacotherapy, Missingness of Variables Included in the Current Analysis by Total, By Those Newly Dispensed Benzodiazepine Pharmacotherapy or Alternative Non-Benzodiazepine Pharmacotherapy.

Covariate	Total (%)	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)
Sex	0.00	0.00	0.00
Age	0.00	0.00	0.00
Race	8.89	8.90	8.85
Ethnicity	5.22	5.22	5.22
Marital Status	5.04	5.06	4.97
Disability Status	0.13	0.13	0.13
History of homelessness	0.00	0.00	0.00
Tobacco Use Ever	0.00	0.00	0.00
Health Conditions			
Physical Health Conditions			
Acute Pain Injury	0.00	0.00	0.00
AIDS/HIV	0.00	0.00	0.00
Blood Loss Anemia	0.00	0.00	0.00
Cancer (non-melanoma skin)	0.00	0.00	0.00
Cardiovascular Disease	0.00	0.00	0.00
Cerebrovascular Disease	0.00	0.00	0.00
Chronic Lung Disease	0.00	0.00	0.00
Cirrhosis	0.00	0.00	0.00
COPD[15]	0.00	0.00	0.00
Deficiency Anemia	0.00	0.00	0.00
Dementia	0.00	0.00	0.00
Diabetes	0.00	0.00	0.00
End Stage Renal Disease	0.00	0.00	0.00
Heart Disease	0.00	0.00	0.00
Hepatitis	0.00	0.00	0.00
Hemiplegia or Paraplegia	0.00	0.00	0.00
Liver Disease	0.00	0.00	0.00
Migraine	0.00	0.00	0.00
Peptic Ulcer Disease	0.00	0.00	0.00
Peripheral Vascular Disease	0.00	0.00	0.00
Pulmonary Circulation Disorders	0.00	0.00	0.00
Rheumatic Disease	0.00	0.00	0.00
Syncope	0.00	0.00	0.00
Sleep Disorders			
Apnea	0.00	0.00	0.00
Circadian Rhythm Sleep Disorders	0.00	0.00	0.00
Hypersomnia	0.00	0.00	0.00

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 6-6 Continued

Covariate	Total (%)	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)
Insomnia	0.00	0.00	0.00
Isolated Symptoms, Apparently Normal Variants, and Unresolved Issues	0.00	0.00	0.00
Other Sleep Disorders	0.00	0.00	0.00
Parasomnia	0.00	0.00	0.00
Sleep Disorders Associated with Conditions Classifiable Elsewhere	0.00	0.00	0.00
Sleep-Related Movement Disorders	0.00	0.00	0.00
Mental Health			
Attention-Deficit/Hyperactivity Disorder	0.00	0.00	0.00
Anxiety	0.00	0.00	0.00
Bipolar Disorder	0.00	0.00	0.00
Depression	0.00	0.00	0.00
Substance Use Disorders			
Alcohol Use Disorder	0.00	0.00	0.00
Drug Use Disorder	0.00	0.00	0.00
Opioid Use Disorder	0.00	0.00	0.00
Posttraumatic Stress Disorder	0.00	0.00	0.00
Schizophrenia and Psychosis	0.00	0.00	0.00
Suicidal Ideation	0.00	0.00	0.00
Traumatic Brain Injury	0.00	0.00	0.00
Overdose-Related Diagnoses			
Opioid overdose	0.00	0.00	0.00
Current Pain Intensity Rating (average)	48.60	48.68	48.05
Body Mass Index	7.26	7.29	7.01
Health Care Coverage			
Supplemental Health Insurance to VHA Coverage			
Medicare (ever/never)	0.00	0.00	0.00
Health Care Utilization in Past Year			
Number of VA Outpatient Visits			
Inpatient Hospital Admission	0.00	0.00	0.00
Inpatient Procedure	0.00	0.00	0.00
Inpatient Surgery	0.00	0.00	0.00

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 6-6 Continued

Covariate	Total (%)	Alternative Non-Benzodiazepine Pharmacotherapy (%)	Benzodiazepine Pharmacotherapy (%)
Outpatient Procedure	0.00	0.00	0.00
Nursing Home Visit	0.00	0.00	0.00
Military Status			
Service Era	0.93	0.92	0.94
Combat Service	8.21	8.23	8.04
Military Sexual Trauma	1.66	1.65	1.70
Military Branch	13.46	13.46	13.48
Prescription Information (Rx[1] Taken During Follow-Up, Yes/No)			
Anticonvulsant	0.00	0.00	0.00
Antihistamine	0.00	0.00	0.00
Anxiolytic	0.00	0.00	0.00
Buprenorphine (for pain)	0.00	0.00	0.00
Migraine pharmacotherapy	0.00	0.00	0.00
Acetaminophen	0.00	0.00	0.00
Facility urbanicity			
Geography Missing	20.43	20.36	20.88

[1] Rx: prescription

NOTE: No cells are reported representing 10 or fewer veterans.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 6-7 Subgroup and Sensitivity Results—All-Cause Mortality. Among VHA Veterans Consistently Dispensed Opioid Pharmacotherapy, Adjusted All-Cause Mortality Rates and Hazard Ratios Between Individuals Newly Dispensed Benzodiazepine Pharmacotherapy Compared to Those Newly Dispensed Alternative Non-Benzodiazepine Pharmacotherapy.

Sensitivity Analysis	Benzodiazepine Pharmacotherapy Death Rate (All Causes)	Alternative Non-Benzodiazepine Pharmacotherapy Death Rate (All Causes)	Hazard ratio (All Causes)	Lower 95 CI%	Upper 95 CI%
Overall	7,493	4,392	1.706	1.603	1.815
Prescription Coverage					
CMS only	15,530	8,939	1.736	1.604	1.878
DUAL: both VHA / CMS	5,265	3,218	1.636	1.38	1.94
VHA only	5,640	3,284	1.718	1.548	1.905
Sex					
Gender—female	2,995	1,895	1.709	1.605	1.819
Gender—male	7,803	4,566	1.580	1.064	2.346
Age ≤65+					
18–64	3,397	1,966	1.728	1.518	1.968
65+	13,391	8,097	1.653	1.547	1.768
Age (Categorical)					
18–34	*	*	*	*	*
35–54	1,677	1,049	1.599	1.169	2.188
55–74	6,114	3,614	1.691	1.545	1.851
75+	23,882	14,794	1.613	1.492	1.744
Ethnicity					
Hispanic (no)	7,243	4,167	1.669	1.153	2.414
Hispanic (yes)	5,181	3,104	1.738	1.625	1.858
Hispanic (missing)	13,878	9,322	1.488	1.239	1.787
Race					
Race (White)	7,786	4,454	1.748	1.629	1.876
Race (Black)	4,125	2,425	1.701	1.332	2.173
Race (Asian)	*	*	1.479	1.27	1.722
Race (Hawaiian)	5,184	4,162	2.031	0.913	4.516
Race (Native)	5,439	2,678	1.995	0.912	4.363
Race (Multi)	3,689	3,689	*	*	*
Race (Missing)	11,865	8,022	1.247	0.488	3.185
Study Year					
Study Year 2007–2012	6,099	4,260	1.432	1.296	1.583
Study Year 2014–2019	8,799	4,478	1.965	1.795	2.15

* Indicates cell sizes less than 20 veterans and/or suppressed to comply with privacy requirements.
NOTES: No cells are reported representing 10 or fewer veterans. CI = confidence interval; CMS = Centers for Medicare & Medicaid Services; VHA = Veterans Health Administration.

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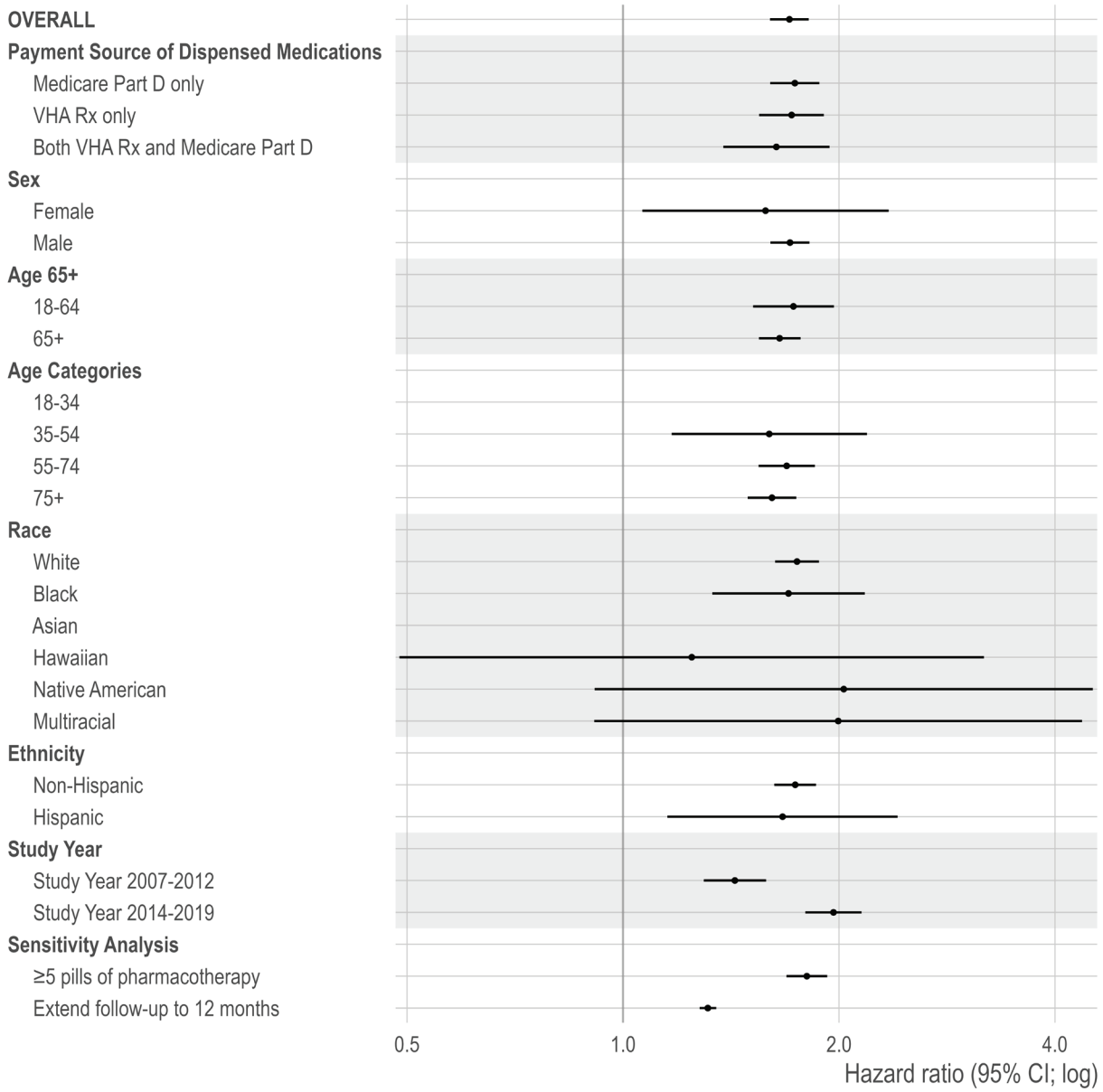

FIGURE 6-6 Among VHA veterans consistently dispensed opioid pharmacotherapy, newly dispensed benzodiazepine pharmacotherapy versus alternative non-benzodiazepine pharmacotherapy on weighted all-cause mortality in subgroup forest plots. NOTE: No cells are reported representing 10 or fewer veterans.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE 6-8 Subgroup and Sensitivity Results—Suicide Mortality. Among VHA Veterans Consistently Dispensed Opioid Pharmacotherapy, Adjusted Suicide Mortality Rates and Hazard Ratios Between Individuals Newly Dispensed Benzodiazepine Pharmacotherapy Compared to Those Newly Dispensed Alternative Non-Benzodiazepine Pharmacotherapy.

	Weighted				
Sensitivity Analysis	**Benzodiazepine Pharmacotherapy Death Rate (Suicide)**	**Insomnia/ Antidepressant Pharmacotherapy Death Rate (Suicide)**	**Hazard ratio (Suicide)**	**Lower 95 CI%**	**Upper 95 CI%**
Overall	117	82	1.416	0.868	2.311
Prescription Coverage					
CMS only	141	125	1.125	0.517	2.448
DUAL: both VHA / CMS	*	30	*	*	*
VHA only	137	77	1.773	0.909	3.456
Sex					
Gender—female	*	*	1.431	0.877	2.337
Gender—male	124	87	*	*	*
Age ≤65+					
18–64	98	68	1.446	0.68	3.073
65+	153	104	1.472	0.794	2.73
Age (Categorical)					
18–34	*	*	*	*	*
35–54	*	51	*	*	*
55–74	97	71	1.358	0.672	2.745
75+	220	156	1.410	0.634	3.136
Ethnicity					
Hispanic (no)	120	78	*	*	*
Hispanic (yes)	*	*	1.540	0.922	2.573
Hispanic (missing)	*	29	*	*	*
Race					
Race (White)	135	85	1.582	0.93	2.69
Race (Black)	*	*	*	*	*
Race (Asian)	*	*	*	*	*
Race (Hawaiian)	*	*	*	*	*
Race (Native)	*	*	*	*	*
Race (Multi)	*	*	*	*	*
Race (Missing)	*	44	*	*	*
Study Year					
Study Year 2007–2012	115	72	1.601	0.769	3.333
Study Year 2014–2019	114	95	1.195	0.557	2.564

* Suppressed to comply with privacy requirements

NOTES: No cells are reported representing 10 or fewer veterans. CI = confidence interval; CMS = Centers for Medicare & Medicaid Services; VHA = Veterans Health Administration.

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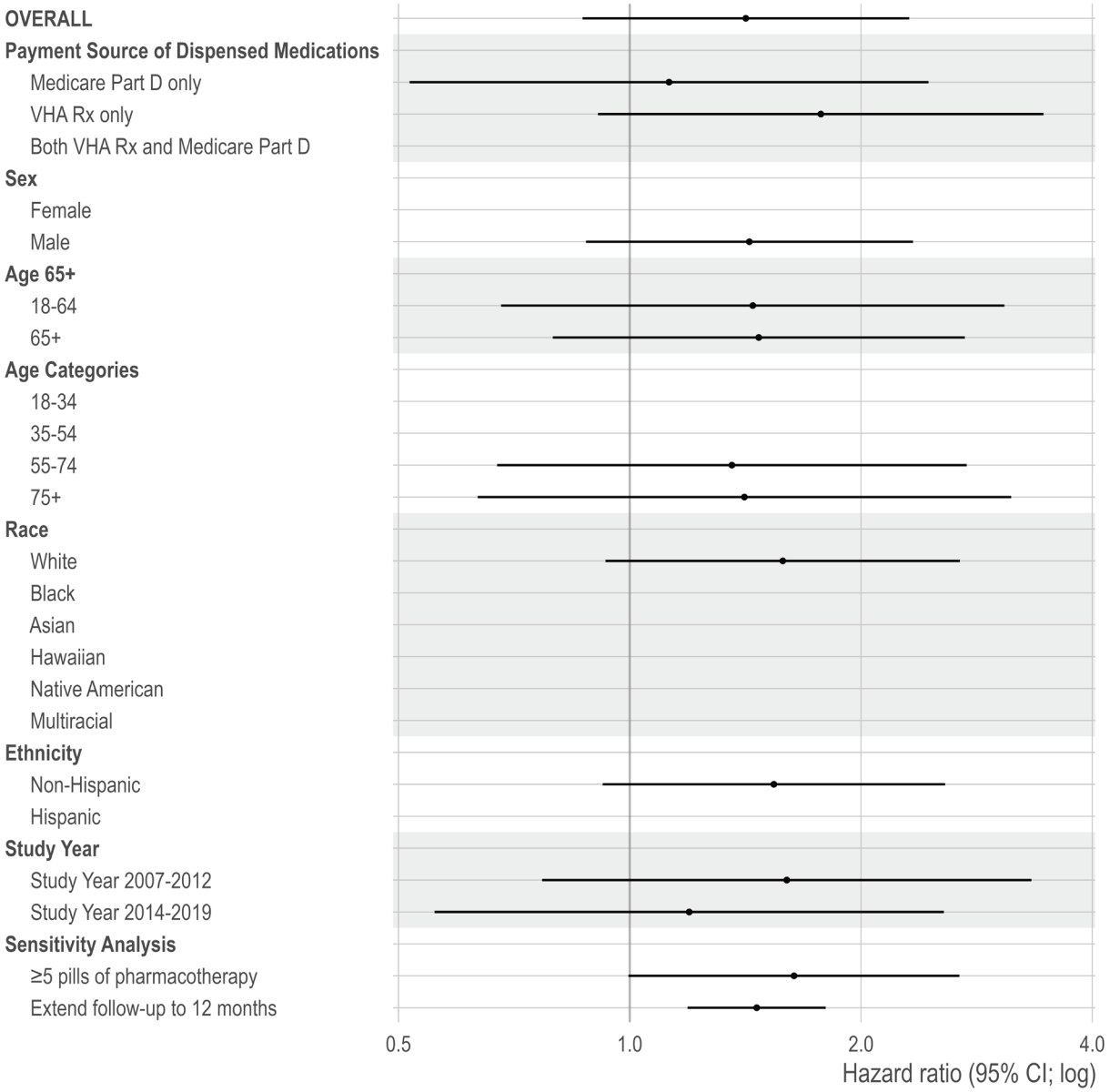

FIGURE 6-7 Among VHA veterans consistently dispensed opioid pharmacotherapy, adjusted hazard ratios of suicide mortality between those newly dispensed benzodiazepine pharmacotherapy versus alternative non-benzodiazepine pharmacotherapy by subgroup.
NOTE: No cells are reported representing 10 or fewer veterans.

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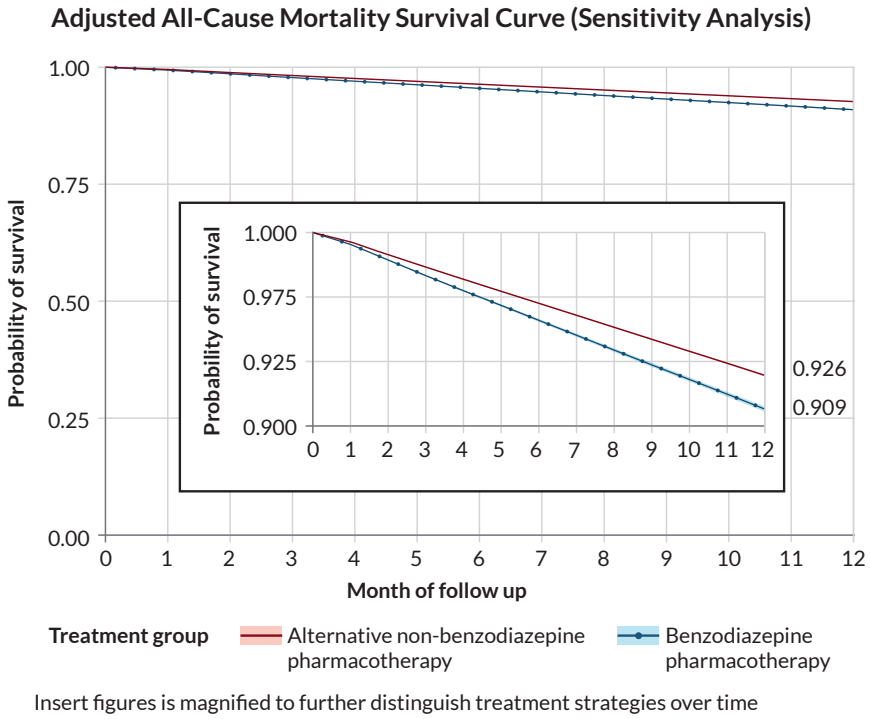

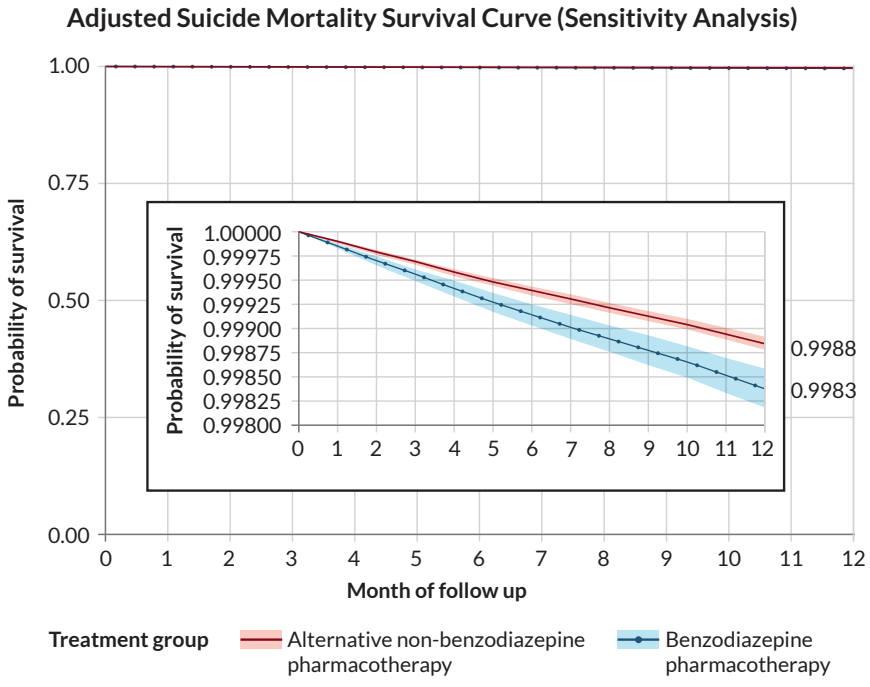

FIGURE 6-8 Among VHA veterans consistently dispensed opioid pharmacotherapy, adjusted survival curves for all-cause mortality (top panel) and suicide mortality (bottom panel) among those newly dispensed benzodiazepine pharmacotherapy versus alternative non-benzodiazepine pharmacotherapy within 12 months (2007–2019).
NOTES: No cells are reported representing 10 or fewer veterans. The y-axis range is compressed on the inset figure.

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A

Committee Member and Staff Biosketches

Brian Strom, M.D., M.P.H. (Chair), is the inaugural chancellor of Rutgers Biomedical and Health Sciences and executive vice president for health affairs at Rutgers University. Although Dr. Strom's interests span many areas of clinical epidemiology, his major research interest is in pharmacoepidemiology, the application of epidemiologic methods to the study of drug use and effects. Dr. Strom is a member of the American Epidemiology Society, American Society of Clinical Investigation, American Association of Physicians, National Academy of Medicine (NAM), and American Association for the Advancement of Science. He received the 2003 Rawls-Palmer Progress in Medicine Award and 2016 Oscar B. Hunter Career Award in Therapeutics from the American Society for Clinical Pharmacology & Therapeutics, Naomi M. Kanof Clinical Investigator Award of the Society for Investigative Dermatology and Sustained Scientific Excellence Award from the International Society for Pharmacoepidemiology. He was the 2008 recipient of the John Phillips Memorial Award for Outstanding Work in Clinical Medicine and the 2013 Association for Clinical and Translational Science/American Federation for Medical Research National Award for Career Achievement and Contribution to Clinical and Translational Science for translation from clinical use into public benefit and policy. Dr. Strom had an advisory role with Jansen Pharmaceuticals/Johnson & Johnson 2017–2019.

Dr. Strom chaired the Institute of Medicine/NAM Committees to Assess the Safety and Efficacy of the Anthrax Vaccine, on Smallpox Vaccine Program Implementation, to Review National Institute for Occupational Safety and Health's Traumatic Injury Program, on the Consequences of Reducing Sodium in the Population, on a National Strategy for the Elimination of Hepatitis B and C, and on Development of a Protocol to Evaluate the Concomitant Prescribing of Opioid and Benzodiazepine Medications and Veterans' Deaths and Suicides. He was a member of the Committee on Standards for Developing Trustworthy Clinical Practice Guidelines and IOM Drug Forum. Dr. Strom earned a B.S. in molecular biophysics and biochemistry from Yale in 1971, an M.D. from Johns Hopkins in 1975, and an M.P.H. in epidemiology at University of California, Berkeley. His residency in internal medicine and fellowship in clinical pharmacology were both at University of California, San Francisco. He was also awarded an honorary Ph.D. from the University of Thrace in Greece.

Amy S. B. Bohnert, Ph.D., is a professor of anesthesiology, executive director for pain and opioid research at the University of Michigan and a research investigator with the Department of Veterans Affairs (VA) Center for Clinical Management Research in Ann Arbor, Michigan. She leads epidemiologic and health services research related to overdose and suicide, prescription drug safety, addiction, and veteran health. Dr. Bohnert was a member

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

of the Stanford-Lancet Commission on the North American Opioid Crisis and has served on Centers for Disease Control and Prevention (CDC) and U.S. Food and Drug Administration (FDA) advisory panels. Dr. Bohnert earned her Ph.D. in public health at Johns Hopkins University and completed her postdoctoral fellowship with the VA National Serious Mental Illness Treatment Research and Evaluation Center in Ann Arbor. Dr. Bohnert also serves as an expert for Michigan to develop an abatement plan to address opioid-related harms in the state. She served on the National Academies of Sciences, Engineering, and Medicine (the National Academies) Committee on Developing a Protocol to Evaluate the Concomitant Prescribing of Opioids and Benzodiazepine Medications and Veteran Deaths and Suicides.

Adam Bress, Pharm.D., M.S., is a formally trained cardiovascular clinical pharmacist and pharmacoepidemiologist. He is a tenured associate professor and vice chair of research for the Department of Population Health Sciences at the University of Utah Spencer Fox Eccles School of Medicine. Dr. Bress is also an investigator at the Department of Veterans Affairs (VA) Salt Lake City Health Care System. His expertise includes the application of causal inference methods to study medication use, responses, and outcomes in large electronic health records and claims databases. He is a National Institutes of Health (NIH)-funded PI, and his team uses causal inference methods in the Veterans Health Administration (VHA) and Kaiser Permanente Southern California data to determine the long-term comparative effects of antihypertensive medications on the risk of dementia, cardiovascular disease, cancer, and frailty. He has successfully designed, led, and published several studies of medication use and effects using VA data. He has substantial experience in building high-quality analysis-ready datasets from VA data and implementing rigorous causal inference methods accounting for time-varying treatment and confounding, out-of-system health care use, and intercurrent events. Dr. Bress received his Pharm.D. from the University of Maryland and his M.S. in clinical and translational science from the University of Illinois–Chicago School of Public Health. He completed his residency in pharmacy practice at Yale-New Haven Hospital and a residency in cardiology and postdoctoral research fellowship at the University of Illinois–Chicago. He was the 2020 National Academy of Medicine Fellow in Pharmacy and a National Heart, Lung, and Blood Institute K-awardee.

Carl A. Castro, Ph.D., M.A., is a professor and director of the Center for Innovation and Research on Veterans and Military Families, Military Veterans Programs at the University of Southern California (USC) Suzanne Dworak-Peck School of Social Work, and USC-RAND Epstein Family Foundation Center for Veterans Policy Research. Dr. Castro joined the faculty in 2013. Before USC, Dr. Castro served in the U.S. Army for over 30 years, beginning as an enlisted infantryman and retiring at the rank of colonel. He held a variety of research and leadership positions, including as director of the Military Operational Medicine Research Program, Headquarters, U.S. Army Medical Research and Materiel Command, Fort Detrick, Maryland. He has completed two tours in Iraq and peacekeeping missions to Saudi Arabia, Bosnia, and Kosovo. Dr. Castro has chaired numerous NATO and international research groups and cochairs a NATO group exploring military and veteran violent radicalization. He is a Fulbright Scholar and member of several Department of Defense research advisory panels focused on psychological health. He has authored more than 300 scientific articles and reports in numerous research areas. His current research efforts focus on assessing the effects of combat and operations tempo on soldier, family, and unit readiness and evaluating service members' transitions from military to civilian life.

Lesley H. Curtis, Ph.D., is professor in the Department of Population Health Sciences in the Duke School of Medicine. A health services researcher by training, Dr. Curtis is an expert in using Medicare claims data for health services and clinical outcomes research and a leader in national data quality efforts. Dr. Curtis has served as co-principal investigor (PI) of the Food and Drug Administration's (FDA's) Sentinel Innovation Center and coinvestigator of the Data Core for the FDA's Sentinel Initiative to monitor the safety of FDA-regulated medical products and the coordinating center for PCORI's National Clinical Research Network (PCORnet). She is co-PI of the National Institutes of Health Pragmatic Trials Collaboratory, an effort to strengthen the national capacity to implement cost-effective, large-scale research studies that engage health care delivery organizations as research partners. As of July 2023, Dr. Curtis is supporting the FDA Office of the Commissioner's initiative to improve national systems for evidence generation.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Patience Moyo Dow, Ph.D., is an associate professor of health services, policy, and practice at the Brown University School of Public Health. Dr. Dow's research focuses on the management of pain and opioid use disorder and often includes using large administrative databases to conduct epidemiologic and policy analyses relating to health services use, quality of care, and outcomes. She also carries out qualitative research focused on understanding post-acute and long-term care use by individuals with opioid use disorder. Between 2020 and 2022, Dr. Dow collaborated with researchers at the Philadelphia VA Medical Center and Providence VA Medical Center to study opioid prescribing patterns among veterans with cancer and outcomes of VA-purchased care in the community; respectively. As of September 2023, she has an active interagency personnel agreement appointment with the Providence VA Medical Center on a project related to homelessness and long-term care among veterans. She earned her Ph.D. in pharmaceutical health services research from the University of Maryland Baltimore and completed her postdoctoral training with the Health Policy Institute at the University of Pittsburgh and the Center for Health Equity Research and Promotion at the VA Pittsburgh Healthcare System.

John T. Farrar, Ph.D., M.D., M.S., is professor of epidemiology, neurology, and anesthesiology and critical care at the University of Pennsylvania Perelman School of Medicine. He received his M.D. from the University of Rochester School of Medicine and his Ph.D. in pharmaco-epidemiology from the Perelman School of Medicine. He is a board-certified neurologist with a subspecialty in pain medicine who has spent his career studying pain, pain measurement, and pain therapies. He has conducted clinical trials and specializes in using large patient datasets in his research, publishing over 200 articles. He has been continuously funded through the National Institutes of Health and the Food and Drug Administration (FDA). He has been a member of several National Academies committees, including the National Academy of Science Panel, Handling Missing Data in Clinical Trials (2009–2010); IOM Committee, Report on Relief of Pain in America (2010–2011); and National Academies Panel, Report on Compounded Topical Pain Creams (2019–2020). He has served as a standing member and then chair of the FDA Anesthetic and Life Support Drugs Advisory Board.

Robert Kerns, Ph.D., M.A., is senior research scientist in the Yale School of Medicine Department of Psychiatry and professor emeritus, Yale University. Dr. Kerns retired from the Department of Veterans Affairs (VA) in 2016 after 38 years of service; he held several leadership positions, including director of the Pain Research, Informatics, Multimorbidities, and Education (PRIME) Center of Innovation (2008–2016) at the VA Connecticut Healthcare System and national program director for pain management (2005–2013). He is a director of the NIH-DOD-VA Pain Management Collaboratory Coordinating Center that supports 14 pragmatic clinical trials of nonpharmacological approaches to manage pain and common co-occurring conditions in military and veteran health systems. His scholarly and scientific contributions focus on comprehensive pain assessment, nonpharmacological approaches for pain management, individual differences and disparities in pain care, safe and effective opioid therapy, and organizational improvements in pain care. Through an IPA between Yale and the VA, Dr. Kerns is a subject matter expert and research investigator at VA's PRIME Center in West Haven, Connecticut. He has received numerous honors and awards, including the 2006 VA David M. Worthen Award for Academic Excellence and Mark Wolcott Award for Clinical Leadership, 2010 John and Emma Bonica Public Service Award, and 2017 Wilbert E. Fordyce Clinical Investigator Award from the American Pain Society. He served as a member of the IOM Committee for Advancing Pain Research, Care, and Education. He received his undergraduate degree in psychology at West Virginia University in 1974 and his Ph.D. in bio-clinical psychology at Southern Illinois University in 1980.

Mathew Kiang, Sc.D., M.P.H., is an assistant professor in the Department of Epidemiology and Population Health at Stanford University School of Medicine. He is a computational social scientist and social epidemiologist whose research focuses on socioeconomic and racial/ethnic inequities in health, especially around substance use and mortality. His recent work has examined how the COVID-19 pandemic has impacted U.S. opioid-related mortality. His NIH-funded projects examine ways to improve initiation and retention in treating opioid use disorder (OUD) and leverage novel data sources to predict opioid-related mortality. Dr. Kiang received his Ph.D. in quantitative methods and social epidemiology from the Harvard T.H. Chan School of Public Health in the Department of Social and Behavioral Sciences and M.P.H. from New York University. Dr. Kiang was a postdoctoral research fellow at

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

the Stanford Systems Neuroscience and Pain Laboratory and a 2016 fellow in the Data Science for Social Good fellowship at the University of Chicago.

Hsien-Chang Lin, Ph.D., M.A.E, M.A., is a professor of health behavior and policy and chair of the Department of Child and Family Development at San Diego State University. Dr. Lin has a strong research program in the prevention, treatment, and effect of substance use behaviors and how the health care system interplays. Leveraging his expertise and research experiences in substance use and pharmacoepidemiology, he has conducted several studies examining physicians' prescribing practice and patients' use/misuse of opioid and benzodiazepine pharmacotherapies among patients with chronic pain and how the health care system and health care policy influence these behaviors. His research has important mental and psychological health aspects, including the investigation of substance use behaviors among people with mental health conditions, the psychological pathways through which risk factors and substance use behaviors are connected, the effect of substance use on affect, and how emotion dynamics are associated with substance use. Dr. Lin is active in the profession. He recently served as president of the American Academy of Health Behavior, where he is a fellow. He is also a fellow of the New York Academy of Medicine. Dr. Lin has received interdisciplinary education and training from National Taiwan University and the University of Michigan, encompassing economics (B.A. and two M.A.s), sociology (B.A.), health care system and policy (Ph.D.), pharmacoepidemiology (Ph.D.), and health outcomes research (postdoctoral fellowship).

Miguel Marino, Ph.D., is professor of biostatistics at Oregon Health & Science University. Dr. Marino's current research interest lies in population-based studies using large administrative observational data sources and electronic health records (EHRs), including developing and implementing novel statistical methodology to address complexities associated with the use of EHRs to study changes in health policy and delivery (e.g., Affordable Care Act, preventive guideline changes, opioid prescribing over time) and validation of EHRs as a reliable source for rigorous observation studies. Dr. Marino's research also focuses on understanding of equitable primary care delivery in underserved populations (Latino individuals, racial/ethnic minorities, etc.) and in methods for data disaggregation among Latino individuals, to better understand the association of Latino nativity with health outcomes. His contributions to primary care and community-based research were recognized by NAM when it selected him in 2020 as one of 10 Emerging Leaders in Health and Medicine Scholars and elected him as a member in 2022. Dr. Marino is a statistical editor for *JAMA Health Forum*. He holds a Ph.D. in biostatistics from Harvard University, an M.S. in biostatistics, and a B.S. in mathematics from UCLA.

Anne Marie McKenzie-Brown, M.D., is interim chair of the Department of Anesthesiology, vice chair for professional development, and a professor at Emory University. She is board certified in anesthesiology and pain medicine. After anesthesiology residency at Emory University, she returned to Johns Hopkins and did fellowship training in pain medicine before returning to Emory on faculty. She was the initial program director of the Emory Multidisciplinary Pain Fellowship for 14 years; it trains future pain physicians from multiple specialties together to become the best pain practitioners and educators. She was the division chief of Emory's Pain Division and medical director of its Pain Center for almost 20 years and is vice chair of professional development in its Department of Anesthesiology. She is a member of many professional organizations, including the American Society of Interventional Pain Physicians, American Society of Regional Anesthesiology and Pain Medicine, American Society of Anesthesiology, and Spinal Injection Society. She is a senior board examiner and member of the American Board of Anesthesiology. Dr. McKenzie-Brown's interests include the treatment of neck and back pain using nonopioid therapies, including interventional pain therapies, such as spinal cord and peripheral nerve stimulation, and complementary therapies for pain. Her goal is to use opioid-free techniques to relieve pain in a healthy way.

Katie J. Suda, Pharm.D., M.S., is a tenured professor at the University of Pittsburgh Schools of Medicine and Pharmacy, clinical pharmacy specialist, research health scientist, and associate director with the VA Center for Health Equity Research and Promotion. Dr. Suda is a national expert in outpatient prescribing patterns and antibiotic stewardship. Her research interests include antimicrobial and opioid pharmacoepidemiology and the effectiveness

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

of implementation strategies to improve prescribing. Dr. Suda has received over $15 million in awards as PI and coinvestigator from AHRQ, CDC, FDA, NIH, and VHA. Her research has informed national policy on outpatient opioid stewardship, provision of VA data to state prescription drug monitoring programs, and the importance of dental prescribing in identifying solutions to the opioid epidemic; she participated on an American Dental Association guideline panel on acute pain oral management released in 2023. She also published a study using 2018 data that examines opioid poisoning among veterans by race and ethnicity. Dr. Suda has served on committees and expert panels focused on evidenced-based prescribing for multiple federal agencies and professional organizations. She has received awards for teaching and research, including the CDC Shepard Science Award and SHEA Antimicrobial Stewardship Scholar Award. Her training includes a Pharm.D., M.S. in epidemiology, and postdoctoral training focused on pharmacoepidemiology.

STAFF

Donna Almario Doebler, Dr.PH., M.S., M.P.H., is a senior program officer at the National Academies of Sciences, Engineering, and Medicine. She is part of the Health and Medicine Division's Board on Population Health and Public Health Practice. Prior to joining the National Academies, Dr. Doebler was the associate vice president of Medicare Advantage at UPMC Health Plan in Pittsburgh, Pennsylvania, where she led product, strategy, and financial and clinical analytics to help manage the care of over 200,000 member lives. In addition, she worked with UPMC hospitals to develop the first community health needs assessments and implementation plans, as part of new requirements of the Affordable Care Act for all non-profit hospitals. Dr. Doebler was also an assistant professor at the University of Pittsburgh Graduate School of Public Health, and worked at the Institute of Medicine and the U.S. Government Accountability Office. Dr. Doebler completed a Kellogg Health Scholars postdoctoral fellowship, has a Dr.PH. in behavioral and community health sciences, an M.S. in biostatistics—both from the University of Pittsburgh, and an M.P.H. in epidemiology from the George Washington University.

Aashaka Shinde, M.A., M.S.P.H., is a associate program officer of the Board on Population Health and Public Health Practice in the Health and Medical Division at the National Academies of Sciences, Engineering, and Medicine (the National Academies). Ms. Shinde graduated from the Johns Hopkins Bloomberg School of Public Health with a focus on social and behavioral interventions. During her graduate studies Ms. Shinde conducted field research on a variety of topics pertaining to health care access. In her work at the National Academies, Ms. Shinde has contributed to a study on the effects of antimicrobial resistance on human and animal health as well as another study on the reassessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry. She also worked on studies focused on maternal and child health research prior to joining the National Academies.

Emma Fletcher, M.S.P.H., is a research associate of the Board on Population Health and Public Health Practice in the Health and Medical Division at the National Academies of Sciences, Engineering, and Medicine. Ms. Fletcher graduated from Johns Hopkins Bloomberg School of Public Health with a focus on Health Systems. During, and following, her graduate studies, Ms. Fletcher conducted field research in peri-urban Lima, Peru, investigating the effect of COVID-19 on infant and child nutrition. Ms. Fletcher also assisted in investigating the impact of COVID-19 on the provision and utilization of health services as well as community health worker programs in West Java, Indonesia. Prior to her graduate degree, Ms. Fletcher obtained a B.Sc. in Population Health from University College London.

Mia Saltrelli, B.S., is a senior program assistant of the Board on Population Health and Public Health Practice in the Health and Medical Division at the National Academies of Sciences, Engineering, and Medicine. Ms. Saltrelli graduated from Furman University with a Bachelor of Science in Public Health.

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Rose Marie Martinez, Sc.D., has been the senior board director of the Board on Population Health and Public Health Practice (BPH) at the National Academies of Sciences, Engineering, and Medicine (the National Academies) since 1999. BPH addresses the science base for population health and public health interventions and examines the capacity of the health system, particularly the public health infrastructure, to support disease prevention and health promotion activities, including the education and supply of health professionals necessary for carrying them out. BPH has examined such topics as the safety of childhood vaccines and other drugs, systems for evaluating and ensuring drug safety post-marketing, the health effects of cannabis and cannabinoids, the health effects of environmental exposures, population health improvement strategies, the integration of medical care and public health, women's health services, health disparities, health literacy, tobacco control strategies, and chronic disease prevention, among others. Dr. Martinez was awarded the 2010 Institute of Medicine (IOM) Research Cecil Award for significant contributions to IOM reports of exceptional quality and influence. Prior to joining the National Academies, Dr. Martinez was a senior health researcher at Mathematica Policy Research (1995–1999), where she conducted research on the impact of health system change on public health infrastructure, access to care for vulnerable populations, managed care, and the health care workforce. Dr. Martinez is a former assistant director for health financing and policy with the U.S. General Accountability Office, where she directed evaluations and policy analysis in the area of national and public health issues (1988–1995). Her experience also includes 6 years directing research studies for the Regional Health Ministry of Madrid, Spain (1982–1988). Dr. Martinez is a former president of the Council on Education for Public Health, the accreditation body for schools of public health and public health programs. She received the degree of Doctor of Science from the Johns Hopkins School of Hygiene and Public Health.

NATIONAL ACADEMY OF MEDICINE FELLOW

Sterling Haring, M.D., Dr.PH., is as an interventional pain physician in South Georgia and served as a Fellow with the National Academy of Medicine. Dr. Haring's research, policy work, and advocacy have been centered on injury issues such as opioids, traumatic brain injury (TBI), and childhood injuries. He worked as a clinical counselor and later administrator in a methadone clinic in South Florida in the mid-2000s, where he worked with local community leaders to try to expand access to addiction treatment. During and after his medical training, he pursued an MPH and Dr.PH. at the Johns Hopkins Bloomberg School of Public Health and served as a fellow at the Center for Surgery and Public Health, a joint venture between the Harvard School of Medicine, Harvard T.H. Chan School of Public Health, and Brigham and Women's Hospital. He completed an epidemiology training program as a part of the TBI team at the Centers for Disease Control and Prevention before spending a year working on issues at the intersection of health care quality and communication in southern Switzerland. After returning to the United States, he completed residency training in physical medicine and rehabilitation, as well as fellowship training in pain medicine, both at Vanderbilt University. There, he was inducted into the Gold Humanism Honor Society and worked with enterprise leadership on institution-wide efforts to reduce opioid over-prescribing. His research and policy work have included interviews with a variety of television, print, and online media outlets ranging from CNN and The TODAY Show to NPR and The New York Times. In 2019, he was part of a team that won an Indie Book Award for a collection of essays reflecting first-person accounts of gun violence in U.S. schools.

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B

Open Session Meeting Agendas

COMMITTEE ON THE EFFECTS OF OPIOIDS AND BENZODIAZEPINES ON ALL-CAUSE MORTALITY IN VETERANS

February 3, 2023

1:00–1:05pm	**Welcome and Introductions; Conduct of the Open Session** *Brian Strom, Committee Chair*
1:05–2:00	**Charge to the Committee and Background on Section 204a Hannon Act** *David Atkins, VA Research Health Services Research and Development* *Jodie Trafton, Program Evaluation and Resource Center for the VHA Office of Mental Health and Suicide Prevention* *Friedhelm Sandbrink, Pain Management, Opioid Safety and Prescription Drug Monitoring Programs (PMOP), Specialty Care Program Office, Veterans Health Administration*
2:00–2:30	**Overview of Available Data Sources** *Jodie Trafton, VHA Office of Mental Health and Suicide Prevention* *Friedhelm Sandbrink, Acting VHA National Program Director for Pain Management*
2:30–2:45	**Congressional Request** *Emily Blair Rubright, U.S. Senate Committee on Veterans' Affairs*
2:45–3:00	**Public Comments**
3:00	**Open Session Ends**

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March 9, 2023

9:00–9:05am	**Welcome** *Brian Strom, Committee Chair*
9:05–10:05	**Panel: Trends in Opioid and Benzodiazepine Use, Addiction, and Related Overdose** **Secular Trends in Opioid and Benzodiazepine Use** *Christopher Jones, Centers for Disease Control and Prevention*
	Distinguishing Between Effect of Prescription Opioids Versus Synthetic/Illicit Opioids **Sequela of Opioid Addiction, Comorbid Mental Health Conditions, and Suicide Risk** *William Becker, Yale School of Medicine*
10:05-11:00	**Panel: Data and Design Considerations**
10:05–10:40	**Opioid Dose Reduction Trial Emulation** *Erin Krebs, Minneapolis VA Health Care System*
10:40–11:00	**Approaches to Examining Effects of Prescribed Opioid Use** *Corey Hayes, University Arkansas for Medical Sciences* *Bradley Martin, University Arkansas for Medical Sciences*
11:00–11:10	**Break**
11:10–11:30	**Data and Design: Associations Between Stopping Prescriptions and Overdose or Suicide Deaths in U.S. Veterans** *Elizabeth Oliva, Department of Veterans Affairs* *Jodie Trafton, Department of Veterans Affairs*
11:30–12:00	**Panel: Provider and Veteran Perspectives Patients' and Providers' Perspective on Tapering** *Joseph Frank, University of Colorado* ***Perspectives from Veterans' Service Organizations*** *Alex Balbir, Wounded Warrior Project*
12:00 noon	**Open Session Adjourns**

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C

Public Law 116-171

An Act

Oct. 17, 2020

[S. 785]

Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019.
38 USC 101 note.

To improve mental health care provided by the Department of Veterans Affairs, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the ''Commander John Scott Hannon Veterans Mental Health Care Improvement Act of 2019''.

(b) TABLE OF CONTENTS.—The table of contents for this Act is as follows:

…

TITLE II—SUICIDE PREVENTION

SEC. 204. DEPARTMENT OF VETERANS AFFAIRS STUDY OF ALL-CAUSE MORTALITY OF VETERANS, INCLUDING BY SUICIDE, AND REVIEW OF STAFFING LEVELS OF MENTAL HEALTH PROFESSIONALS.

(a) STUDY OF DEATHS OF VETERANS BY SUICIDE.—

(1) IN GENERAL.—The Secretary of Veterans Affairs shall seek to enter into an agreement with the National Academies of Sciences, Engineering, and Medicine under which the Secretary shall collaborate and coordinate with the National Academies on a revised study design to fulfill the goals of the 2019 study design of the National Academies described in the explanatory statement accompanying the Further Consolidated Appropriations Act, 2020 (Public Law 116–94), as part of cur- rent and additional research priorities of the Department of Veterans Affairs, to evaluate the effects of opioids and benzodiazepine on all-cause mortality of veterans, including suicide, regardless of whether information relating to such deaths has been reported by the Centers for Disease Control and Prevention.

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(2) GOALS.—In carrying out the collaboration and coordination under paragraph (1), the Secretary shall seek as much as possible to achieve the same advancement of useful knowledge as the 2019 study design described in such paragraph.

(d) BRIEFINGS.—The Secretary of Veterans Affairs shall brief the Committee on Veterans' Affairs of the Senate and the Committee on Veterans' Affairs of the House of Representatives containing the interim results—

(3) with respect to the study under subsection (a)(1), not later than 24 months after entering into the agreement under such subsection; and

(e) REPORTS.—

(4) REPORT ON STUDY.—Not later than 90 days after the completion by the Secretary of Veterans Affairs in coordination with the National Academies of Sciences, Engineering, and Medicine of the study required under subsection (a)(1), the Secretary shall—

(A) submit to the Committee on Veterans' Affairs of the Senate and the Committee on Veterans' Affairs of the House of Representatives a report on the results of the study; and

(B) make such report publicly available.

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D

Detailed Policy Landscape

THE DEPARTMENT OF VETERANS AFFAIRS/DEPARTMENT OF DEFENSE CLINICAL PRACTICE GUIDELINES

The Department of Veterans Affairs (VA) and Department of Defense (DoD) have several joint clinical practice guidelines (CPGs) on specific health care topics that are evidence based and capture best clinical practice with the goals of reducing variation in care and providing quality care. Topics reflect domains such as pain, mental health, chronic disease in primary care, rehabilitation, and women's health (VA, 2024a). The VA/DoD's stated goal for the CPGs "is to improve the patient's health and well-being by providing evidence-based guidance to providers who are taking care of patients on or being considered for [long-term opioid treatment]" (VA/DoD, 2017). Four CPGs, introduced in 2003 and updated in 2010, 2017, and 2022, address opioid initiation and continuation, dosage, tapering/discontinuation, screening/assessment/evaluation, and risk mitigation (VA/DoD, 2022, 2017, 2010, 2003). Beginning in 2010, the CPGs included literature reviews and graded recommendations based on the evidence.

For opioid initiation, all VA/DoD CPGs recommended beginning with a low or lowest dose. Later CPGs added that "there is no absolutely safe dose of opioids" (VA/DoD, 2017) and recommended against initiating opioid therapy in individuals with chronic non-cancer pain (VA/DoD 2022, 2017). Maximum opioid dose levels were stated in CPG 2010 (a reasonable level of less than 200 morphine milligram equivalents (MME)/day), and VA/DoD CPG 2017 recommended against doses over 90 MME/day for chronic pain.

Opioid pharmacotherapy tapering (reduced dose or discontinuation) guidelines continue to evolve as well. In the first VA/DoD CPG (2003), recommendations to consider tapering were when opioids are not efficacious in managing pain, pain is resolved, or the individual requests this. In addition, discontinuation should be made on an individual basis. The 2010 VA/DoD CPG continued to recommend these indications and added to consider when harms (real or potential) outweigh potential benefits. In VA/DoD CPG (2017), opioid tapering is recommended when risks outweigh the benefits. In addition, discontinuing abruptly is recommended to be avoided. However, the current VA/DoD CPG (2022) noted "insufficient evidence to recommend for or against any specific tapering strategies." In addition, opioid tapering should be patient centered and approached collaboratively. The workgroup noted the low quality of evidence due to limitations in the relevant studies (e.g., differences among treatment groups, lack of certainty in outcomes and treatment adherence) (VA/DoD, 2022). Concerns of interactions with benzodiazepines first appeared in CPG 2010, and subsequent CPGs since 2017 include a recommendation against concurrent use of opioids and benzodiazepines (VA/DoD, 2022, 2017, 2010).

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OTHER AGENCIES

In addition to VA policies and guidelines, other federal agencies followed VA and released guidelines or warnings related to opioid prescribing, tapering, and discontinuation.

Centers for Disease Control and Prevention

Similar to VA, the Centers for Disease Control and Prevention (CDC) release CPGs to provide guidance to clinicians for prescribing opioids for pain. The CDC released the first CPG for the treatment of pain with opioids in 2016, with another in 2022. The CPG included a literature review and guidance on opioid initiation, pain management, and tapering.

The 2016 CDC CPG for Prescribing Opioids for Chronic Pain recommended using the lowest effective dose. Guidelines recommended assessing evidence before increasing above >50 MME/day and avoiding >90 MME/day. The 2016 CPG described a decrease of 10 percent of an original dose per week as a reasonable starting point for tapering. However, all tapering plans should be individualized based on patient concerns and/or goals (Dowell et al., 2016).

In 2022, CDC published an updated CPG that recommended that clinicians prescribing opioids for opioid-naïve patients with pain (acute, subacute, or chronic) should choose the lowest effective dosage, often equivalent to a single dose of about 5–10 MME or a daily dosage of 20–30 MME/day. While the CPG recognized that evidence supporting specific opioid tapering rates is limited and the rate of tapering should be based on the patient's unique clinical situation, opioid tapering of 10 percent per month or slower in patients who have been taking opioids for longer periods are likely to be better tolerated (Dowell et al., 2022).

U.S. Food and Drug Administration Drug Administration

Black Box Warnings

Given the concerns regarding the use and co-prescribing of benzodiazepine and opioid pharmacotherapy, in 2016, the Food and Drug Administration (FDA) added a black box warning to benzodiazepines, opioids, and opioid-containing cough medicines. The warning highlighted the potential dangers of independent or combined benzodiazepine and opioid use (FDA, 2016). Additional information on FDA activities and significant events addressing substance use and overdose prevention can be found in FDA (2024a).

Opioid Analgesic Risk Evaluation and Mitigation Strategy

Through the FDA Amendments Act of 2007, FDA is required to obtain a risk evaluation and mitigation strategy (REMS) from manufacturers to ensure that "benefits of a drug or biological product outweigh its risks" (FDA, 2015). The FDA requires manufacturers of extended-release and long-acting (beginning in 2012) and immediate-release opioid analgesics (beginning in 2018) to implement an opioids REMS. The program is now called the Opioid Analgesic Risk Evaluation and Mitigation Strategy (OA REMS), which serves as an effort at the national and state levels aiming to reduce "the risk of abuse, misuse, addiction, overdose, and deaths due to prescription opioid analgesics" (FDA, 2024b). A core element of the OA REMS is accredited continuing education. OA REMS requires the availability of education to all health care providers involved in pain management and treatment and for drug companies to "provide unrestricted grants to accredited continuing education providers for the development of education courses" (FDA, 2024b).

Centers for Medicare and Medicaid Services

The Centers for Medicare & Medicaid Services also released guidance and education to providers regarding opioid prescribing and co-prescribing with benzodiazepines (CMS, 2019).

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Department of Health and Human Services

In 2019, the Department of Health and Human Services released a guide for clinicians on the "Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics." It does not specify a tapering strategy for clinicians but suggests a reduction of 5–20 percent every 4 weeks (in reference to CDC 2016 and VA/DoD 2017 CPGs). It also highlights a patient-centric approach that is tailored to individual needs and outlines various scenarios in which clinicians could consider tapering or discontinuation (HHS, 2019).

The National Action Plan for Adverse Drug Event Prevention, released in 2014, was established to address two objectives: "1) identify common, preventable, and measurable adverse drug events (ADE) that may result in significant patient harm; and 2) align the efforts of federal health agencies to reduce patient harms from these specific ADEs nationally" (HHS, 2014). Three types of ADEs were deemed "common, clinically significant, preventable, and measurable" and are considered high-priority targets of the plan: anticoagulants (ADE: bleeding), diabetes agents (ADE: hypoglycemia) and opioids (ADE: accidental overdoses/ oversedation/respiratory depression). The ADE Action Plan presents a four-pronged approach to reducing patient harms: surveillance, prevention, incentives and oversight, and research (HHS, 2014).

Veterans Health Administration

The Opioid Safety Initiative

Expanding on the VA safe opioid prescribing strategies, which date back to the 1990s, the Veterans Health Administration (VHA) implemented the Opioid Safety Initiative (OSI) in 2013 "to help decrease prescribing practices associated with adverse outcomes" and promote safer prescribing in VHA (Lin et al., 2017). The OSI goals are increased education, monitoring, safe and effective prescribing and development and implementation of management methods, tool development, collaboration, and use of alternative pain treatments (GAO, 2018). The OSI aimed to reduce overdependence on opioids for pain management in VHA by limiting opioid use to safe and effective doses only when clinically indicated (Lin et al., 2017). The OSI has been integrated into the VHA's electronic health record (EHR) to identify patients who may be at increased risk for adverse outcomes related to use of opioids and providers whose prescribing practices may not reflect best evidence (VA/DoD, 2022). In addition, the OSI was set up around a dashboard using aggregated EHR-based facility-, provider-, and patient-level opioid prescribing data to facilitate leadership audit and feedback (Lin et al., 2017). There are nine key components to the OSI designed to improve patient outcomes (Table 1: GAO, 2018):

1. Educate opioid prescribers regarding the effective use of urine drug screening.
2. Increase the use of urine drug screening.
3. Facilitate the use of Prescription Drug Monitoring Program (PDMP) databases.
4. Establish safe and effective veterans integrated service network (VISN) tapering programs for veterans using opioids and benzodiazepines.
5. Develop tools to identify veterans at a higher risk for adverse events while using opioids.
6. Improve prescribing practices around long-acting opioid formulations.
7. Review treatment plans for veterans on high doses of opioids.
8. Offer complementary and alternative medicine modalities for chronic pain at all medical facilities.
9. Develop new models of mental health and primary care collaboration to manage the prescribing of opioids and benzodiazepines in patients with chronic pain.

Additional OSI efforts include the Opioid Overdose Education and Naloxone Distribution program, a risk mitigation strategy aimed at reducing overdose deaths. The program includes education and training on the following: overdose prevention, recognition, and rescue response; risk mitigation strategies; and issuing naloxone kits, which can be used as an antidote (VA, 2024b,c,d; Oliva et al., 2016). Other efforts include the OSI Toolkit, which

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contains materials to inform clinical decision making regarding opioid pharmacotherapy and safe prescribing, and "Taking Opioids Responsibly for Your Safety and the Safety of Others: Patient Information Guide on Long-Term Opioid Therapy for Chronic Pain" (VA, n.d.).

Research indicates progress in the improvement of opioid safety through the OSI. VHA has met six of the nine OSI goals; however, it is unclear whether the remaining three goals have been fully achieved (GAO, 2018). An assessment of the impact of OSI on opioid prescribing among veterans in 2017 found a decreasing trend in high-dosage prescribing after OSI implementation across the VHA, with a 16 percent reduction in patients receiving daily doses of over 100 MME in 2014 (Lin et al., 2017). Research by Lin and colleagues (2017) investigating the effectiveness of the OSI reported a reduction in both veterans' daily opioid MME and in those receiving concomitant benzodiazepine pharmacotherapy 2012–2014. An assessment of 2012–2020 VHA Pharmacy Benefits management services data found that since the implementation of OSI, the number of veterans being prescribed opioids has reduced by 56 percent, and concomitant prescribing of opioids and benzodiazepines has reduced by 83 percent (Sandbrink et al., 2020).

Recent VHA Directives

VHA issued several directives aiming to achieve department-wide changes in prescriber behaviors that were reflective of changing guidelines and clinical knowledge. VHA Directive 1306, in 2016, required VHA providers to register for their state PDMP, abide by state PDMP law, query the state PDMP for patients receiving a controlled substance prescription for longer than 5 days or for shorter courses with refills (except for hospice care), and document PDMP results in EHRs (Sandbrink et al., 2020; VA, 2016). These queries provide clinicians with a history of controlled substance prescriptions, across all care locations, to inform prescribing decisions (VA, 2016).

VHA Directive 1005 in 2014 required an "Opioid Pain Care Agreement" between the provider and patient. It outlines "the exchange of information between a health care provider and patient regarding the expectations, responsibilities, and obligations of patients to receive opioid therapy" (VHA, 2020) and generally advises patients to take the medications only as directed, adhere to drug testing, not request early refills or replacements, and not use illegal drugs. The updated VHA Directive 1005 in 2020 amended requirements to make patient education and informed consent before opioid prescribing mandatory and prohibit such agreements in the VHA (VHA, 2020). In addition to the outlined VA/DoD CPGs and directives, VHA has implemented additional risk mitigation strategies, such as requiring informed consent before initiating long-term opioid treatment (LTOT), ongoing assessment of opioid effectiveness, the routine urine drug monitoring and pill counts (VA/DoD, 2017).

Relevant Federal Legislation

Veterans Choice Act (2014)[1]

The Veterans Choice Act (also known as "Veterans Choice Program" (VCP)) was passed in 2014. This federal legislation expanded non-VHA service options for veterans to receive care.

Comprehensive Addiction and Recovery Act (2016)[2]

The Comprehensive Addiction and Recovery Act (CARA) became national legislation in 2016. Several aspects were relevant to opioid management within VA. First, CARA directed the VA Secretary to extend the OSI to all VHA-approved non-VHA health facilities. In addition, CARA required that all VHA-approved providers prescribing opioids to VHA veterans be educated on safe opioid prescribing practices, specifically in compliance with CPGs. Third, VA worked to ensure VHA prescribers have access to their own state PDMPs. Finally, through

[1] Public Law 113-146, 113th Congress, Veterans access, Choice and Accountability Act of 2014, August 7, 2014.
[2] Public Law 114-198, 114th Congress, Comprehensive Addiction and Recovery Act of 2016, July 22, 2016.

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the extension of OSI practices, all VHA-approved providers were required to submit veteran prescription fills of controlled substances from VHA pharmacies to state PDMPs.

Mission Act (2018)[3]

In 2018, Congress passed the Mission Act, which was designed to strengthen and improve the quality of the VHA system and improve timely access to quality care. This expanded ongoing efforts by VHA to enable veterans to access non-VHA facilities to receive health care, with VHA covering the costs, including non-urgent care outside VHA and local non-VHA community facilities. The Mission Act established the Veterans Community Care Program (VCCP), which replaced the VCP. The VCCP enabled eligible veterans to receive care from community providers in the regional network, paid for by VA, when VA cannot provide it.

Relevant State Level Policies and Contributions

Prescription Drug Monitoring Programs

PDMPs are designed to facilitate the collection, analysis, and reporting of controlled drug prescribing and dispensing within a state (Brandeis University, 2018). Through the PDMP, registered clinicians can obtain information on patients receiving controlled medications, other providers prescribing controlled medications, prescribed dosages, date dispensed, and name of prescribing clinician. States implemented the PDMPs at various times. California was the first state to do so, in 1939. Additional states followed (eight in 1990, 27 in 2000–2010). As of 2023, Missouri is the only state without fully operational PDMP legislation; however, a statewide PDMP has been activated (Missouri PDMP, 2023; Brandeis University, 2018; Clark et al., 2012). The PDMP is intended to mitigate risks in opioid prescribing through monitoring; however, complexities in the effective use of PDMPs remain (Rhodes et al., 2019; VA OIG, 2019).

Given that many veterans use more than one health care system, PDMPs can help monitor prescribing of controlled medications, especially among veterans obtaining care in the VHA and through non-VHA providers (Carico et al., 2018; Gellad et al., 2018; Becker et al., 2017; Park et al., 2015). In 2012, 13.2 percent of eligible veterans dually enrolled in VHA and Medicare Part D insurance received prescribed opioids from both sources (Gellad et al., 2018). VHA veterans were more likely to be queried in the PDMP if they were ethnically Hispanic, resided in an urban area, received methadone, had average daily MMEs >20, or received a urine drug screening during the study period (Andrea et al., 2021). Veterans less likely to be queried were those who had a rural address, received mail order medications, had a cancer diagnosis, or had a provider working in in a low-complexity facility (Andrea et al., 2021).

Continuing Provider Education

Several efforts exist to promote continuing education (CE) of providers involved in pain management and treatment. As mentioned earlier, FDA's OA REMS program is an example of efforts ongoing at the federal level. In addition, states also require CEs of providers, such as physicians and dentists, to maintain licensure (Xu et al., 2017). Additional information on provider education can be found in *Educating Together, Improving Together: Harmonizing Interprofessional Approaches to Address the Opioid Epidemic* (NASEM, 2021).

[3] Public Law 115-182, 115th Congress, VA Mission Act of 2018, June 6, 2018.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

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E

Opioid Tapering and All-Cause Mortality, Including Suicide Mortality

INTRODUCTION

The committee was tasked with evaluating the relationship between prescribed opioid exposure and all-cause mortality among veterans. As explicitly stated in the statement of task, one of the studies conducted by the committee focused on the effect of opioid escalation on mortality. The statement of task did not direct the committee to examine the effect of opioid tapering on mortality. However, tapering among those taking opioids long term is one potential aspect that could impact mortality risk. Opioid tapering practices are almost always driven by clinicians' individual-specific concerns, which are often not well documented (e.g., potential opioid misuse behaviors do not have an International Classification of Diseases code and may not be reflected in electronic health records). The committee notes that differences in opioid escalation practice are often due to clinical practice variation and adequate control of pain at the current dose, captured through time-varying pain intensity rating, which the committee does in study 2, Chapter 6 (effect of opioid escalation on all-cause mortality and suicide mortality).

In this report, the committee reviewed the work and opioid tapering protocol developed by the 2019 National Academies of Sciences, Engineering, and Medicine (the National Academies) committee. That committee determined that tapering was increasingly common in clinical practice, with clinical uncertainty around it. Specifically, it noted that it was unclear whether tapering to avoid known adverse events of opioid use, such as mortality, was safer than not doing so, given the increased risk of adverse events, such as suicide, that could be precipitated by stopping treatment, especially for individuals who are dependent on opioids. Anecdotal reports of individual harm resulting from discontinuation and tapering had emerged, but little empirical research had been conducted on the topic (Covington et al., 2020). Before attempting to implement the 2019 protocol or a revised one, the committee commissioned a review examining the effect of opioid tapering on mortality, the methodological limitations and study design issues, and currently funded randomized controlled trials examining opioid tapering. The appendix concludes with the committee's observations on the potential utility of these studies in examining the causal effect of opioid tapering on all-cause mortality, including suicide mortality.

2019 NATIONAL ACADEMIES COMMITTEE'S OPIOID TARGET TRIAL TAPERING PROTOCOL

The National Academies (2019) proposed target trial for opioid tapering included eligibility criteria of individuals with long-term opioid treatment (LTOT) (3+ opioid prescriptions dispensed ≥21 days apart in an ≥84-day

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period for ≥84-day supply) with an average opioid morphine milligram equivalent (MME)/day of ≥30 over the prior 84 days. Eligible individuals would all be receiving long-term benzodiazepine pharmacotherapy. Individuals would be randomized to one of four opioid tapering treatment strategies (a) no reduction (≤5 percent average decrease per month for 3 months), (b) slow reduction (>5 percent to ≤10 percent average decrease per month for 3 months), (c) moderate to fast reduction (>10 percent average decrease per month for 3 months), and (d) complete discontinuation within 3 months from baseline. The committee noted that "there is a lack of primary literature on the optimal rate of tapering speed." Start of follow-up would begin at baseline, and individuals would be followed for 6 months. Outcomes of interest were all-cause and suicide mortality. Causal contrast is intent-to-treat and per protocol effects. In terms of statistical analysis, the 2019 committee noted that an individual's baseline data may correspond to any of the opioid treatment strategies. One approach to address this is to create a clone of each strategy for each individual. The 2019 committee identified several challenges in developing the opioid tapering protocol, including "the appropriate classification of the intervention categories represents a specific challenge as it requires inference of the intended treatment strategy (e.g., continuation, slow taper, fast taper) from multiple consecutive prescription fills" and that guidelines and prescribing practices continue to evolve (see also Chapter 2 or Appendix D for more details regarding policy changes).

SUMMARY OF OPIOID TAPERING STUDIES

In the few years since the publication of the 2019 National Academies report, there have been a number of observational studies on opioid tapering. In evaluating the published literature, the committee commissioned a systematic review conducted by the University of Pennsylvania's Penn Medicine Center for Evidence-Based Practice (CEP), which appears as a supplement at the end of this appendix. The review was conducted in November 2023, and identified 31 studies of opioid tapering in U.S. adults. The majority of these studies were published after the National Academies report (2019), with 22 during 2019 or later. The review applied standard methods to assess the scientific rigor and potential for bias of the studies. The committee noted that this approach is relatively conservative, in that the overall risk-of-bias rating can be no better than the lowest component rating. Many of the 31 observational studies were considered to have a "moderate" risk of bias, indicating that the designs were sound but not equivalent to a randomized controlled trial (RCT). Three studies reported all-cause mortality as an outcome (Binswanger et al., 2022; James et al., 2019; Krebs et al., unpublished), and only the Krebs study reported suicide mortality as an outcome (see Table E-1); all were evaluated as having a "moderate" risk of bias (see Annex). The unpublished study was presented and discussed with the committee in a public session; it was commissioned by the Department of Veterans Affairs (VA) to specifically carry out the 2019 National Academies opioid tapering trial protocol and appears in Appendix F of this report.

The studies suggest that opioid tapering was not associated with all-cause mortality (James et al., 2019; Binswanger et al., 2022; Krebs et al., unpublished) (see Table E-1). Both James and colleagues (2019) and Binswanger and colleagues (2022) were retrospective cohort designs. The Krebs study was an emulated opioid tapering trial using retrospective observational data from a cohort of individuals with LTOT for chronic pain and in VA primary care. The study examined two dose reduction strategies—small and large—and compared to those with no dose reduction over 12 months. Outcomes of interest were all-cause and suicide mortality. The results demonstrated no difference in all-cause mortality between a small versus no dose reduction (aHR[1]: 1.01; 95% CI[2]: 0.98–1.04). There was a statistically significant increase in all-cause mortality risk between those with a large versus no dose reduction (aHR: 1.23; 95% CI: 1.20–1.27). For suicide mortality, comparing either small or large dose reduction to those with no dose reduction resulted in no significant difference. It was noted that the study's findings and conclusions were highly sensitive to different study design, statistical modeling, and measurement strategies. In addition, the treatment assignment was based on pharmacy records and as such may not accurately reflect whether a tapering was intended or actually took place.

[1] aHR: adjusted hazards ratio.
[2] CI: confidence interval.

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TABLE E-1 Studies Examining the Effect Opioid Tapering On All-Cause and Suicide Mortality

Study and Population	Results	Overall Risk of Bias
	All-Cause Mortality	
Binswanger et al., 2022 *N* = 3,913 Non-veterans	Decreasing dose trajectory, compared to stable trajectories, was not associated with all-cause mortality. aHR: 1.28; 95% CI: 0.87–1.86.	Moderate
James et al., 2019 *N* = 572 Non-veterans	Discontinuation was not associated with a significant risk for all-cause mortality. HR: 1.35; 95% CI: 0.92–1.98; $p = 0.122$.	Moderate
Krebs et al., unpublished *N* = 207,204 Veterans	No difference was reported in risk of all-cause mortality between small dose reduction group and control group. HR: 1.01; 95% CI: 0.98–1.04. Large dose reduction group had a small, statistically significant increase in all-cause mortality risk compared to the control group. HR: 1.23; 95% CI: 1.20–1.27.	Moderate
	Suicide Mortality	
Krebs et al., unpublished *N* = 207,204 Veterans	No difference in risk of suicide mortality was reported for small dose reduction group versus control group. HR: 1.09; 95% CI: 0.89–1.35. No difference in risk of suicide mortality was reported for large dose reduction group versus control group. HR: 1.01; 95% CI: 0.77–1.33. Individuals who died during 1-year follow-up had no difference in risk of suicide mortality (as opposed to other cause of death) for either treatment comparison.	Moderate

NOTES: aHR = adjusted hazard ratio; CI = confidence interval; HR = hazard ratio.

Based on the presentation and discussion with Dr. Krebs and review of the two study results, the committee learned that the findings and conclusions of these studies are highly sensitive to study design, statistical modeling, and measurement choices. In the Krebs unpublished paper, additional limitations include that the treatment assignment of an individual was based on information at a point in time and may not reflect the dynamic nature of treatment strategies. Additional factors may also not be reflected, such as multiple and overlapping opioid prescriptions. Unmeasured confounding may still exist (such as discontinuation due to opioid misuse or clinical indications, which are not well reflected in clinical or administrative data). In other words, study results and conclusions vary substantially based on the choices made by researchers, even within a set of choices that are all reasonable. Because studies used different definitions of tapering and discontinuation and a wide range of designs, the committee felt that caution should be taken in directly comparing the effect estimates from the different studies.

In evaluating these opioid tapering studies, many on the committee raised concerns of entrenched problems that cannot be overcome when studying a clinical question so complex and ill defined, concerns that were also noted as limitations in the 2019 report. Most notable is a high potential for the presence of confounders that cannot be fully measured because the decision to taper or discontinue opioids is often driven by factors that are themselves causes of early death, such as developing opioid misuse or addiction. In addition, treatment selection bias can occur if the individuals who taper are intrinsically different from those who do not. That is very likely to be true of this research question, as the decision to taper or discontinue is often driven by individual behavior, such as risky opioid use, or adverse effects (Lovejoy et al., 2017).

Documentation of these confounding factors is likely incomplete. Significant challenges also arise with immortal time bias—which stems from using post-baseline treatment information for treatment group assignment. Specifically, aligning eligibility, treatment assignment, and the start of follow-up is essential to avoid immortal time and other key biases in observational research (Hernán et al., 2016). Tapering is measured through refills of decreasing dosage and, by definition, requires follow-up time to observe refills, making it impossible to align these

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three-time anchors to the same day. Designs such as clone-censor-weight and parametric G-formula can address this misalignment, as in other studies in the report, but these were used in very few of the reviewed studies. These problems have become more evident as multiple independent research groups carried out work in this area. In the next section, the committee considers these problems in greater detail.

LIMITATIONS AND CHALLENGES OF OPIOID TAPERING TARGET TRIAL

The committee notes several limitations and/or challenges in designing the opioid tapering target trials using retrospective observational data to infer causality, including immortal time bias, treatment selection bias, and measurement bias (misclassification of the intervention and/or outcomes).

Immortal Time Bias

For any observational study, aligning the timing of the three crucial factors of eligibility, start of treatment, and start of follow-up is critical to avoiding immortal person time and other forms of bias. For opioid tapering, the exact time at which it starts is often ambiguous even when the decision making of the individual with evidence of LTOT and prescriber are known and even more so when ascertained by clinical or administrative records. For example, the prescriber and individual may decide to begin by increasing the time interval between doses, effectively increasing the number of days covered by an existing prescription. In clinical and administrative data, the decision would only become apparent over time when the prescription is refilled. In other words, defining opioid tapering from dose trajectories in administrative records requires post-eligibility follow-up time. If that is concurrent to the time that tapering is being measured, the study will be inherently flawed by immortal person time. This is because future information (refills or lack thereof) is used to retrospectively determine treatment group; the period before enough information is available to classify treatment group is "immortal" because an individual cannot die and be correctly classified. While alternative designs can avoid immortal person time, any misalignment of the three critical time anchors will result in bias. For example, if researchers use a 3-month period to define trajectories based on dispensed opioids (slow, fast, abrupt) and begin follow-up at the end of the 3 months, this avoids immortal person time. However, it conditions the analysis on surviving the 1-month treatment strategy identification period, which introduces selection bias. A particularly problematic form of selection bias occurs when immortal person time exists for some treatment groups but not others, such as when the days covered by dispensed opioids have lapsed with no immediate refill. Without future information on opioid refills, it can be impossible to distinguish whether this is the beginning of a discontinuation or a meaningless gap caused by non-consecutive pharmacy dispensed dates. However, using future refill information could result in immortal time for only those ultimately deemed to be continuing opioids, and treatment would appear safer than it is. The direction of the bias caused by the immortal time will vary depending on the specifics of the treatment group definitions but can be severe enough to "flip" the direction of the relationships.

When data at time zero are insufficient to assign a treatment strategy, a number of general approaches exist to handle this issue without inducing bias: randomly assign the individual to a strategy consistent with their treatment (slow, fast, or abrupt), create exact copies ("clones") of the individual for each possible strategy that their data are consistent with at that time and censor observations when the prescription data are no longer consistent with a given treatment strategy, or use the parametric G-formula (as in study 2, Chapter 6) (Hernán and Robins, 2016). The committee notes that the clone approach, which was recommended by the 2019 report, was used in a small number of the studies included in the synthesis presented earlier in this appendix.

Treatment selection bias can occur if the individuals who taper are intrinsically different from those who do not. That is very likely to be true of this research question (Lovejoy et al., 2017). Documentation of these confounding factors is likely incomplete. For example, tapering could be more likely for individuals with uncontrolled psychiatric symptoms not noted in the medical records or less likely for individuals with pain and comorbid psychiatric symptoms that are being actively treated.

Misclassification of opioid tapering (intervention). The intervention strategy for tapering (slow, fast, abrupt) is inferred from dispensed prescription information. This is necessary to examine outcomes such as all-cause and suicide mortality, which require large sample sizes that would not be possible to achieve under study designs that

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ascertain treatment choice through more direct means. However, consecutive dispensed prescription information may not coincide with the intended strategy, which could lead to misclassification bias of exposure.

In summary, given the challenges in the design of retrospective observational studies, and the risk of immortal time and selection biases, the committee finds that these challenges and limitations substantially limit how well such studies can infer causality between opioid tapering and mortality and are likely to contribute to inconclusive results. For this reason, the committee chose not to implement the tapering trial suggested in the 2019 report.

SUMMARY OF ONGOING RANDOMIZED CLINICAL TRIALS

Given the concerns about unmeasured confounding in observational designs, the committee reviewed databases (NIH RePORTER, PCORI Portfolio, and ClinicalTrials.gov) of currently funded studies and identified several ongoing and/or recently completed RCTs that directly or indirectly test opioid tapering protocols in June 2024, including 14 ongoing RCTs of various tapering interventions on long-term opioid use (see Table E-2). Three trials directly compare the effectiveness of different tapering protocols, and six trials will examine the effect of pharmacotherapies (buprenorphine, buspirone, tizanidine) on opioid reduction. Six trials will assess the effectiveness of cognitive behavior therapy interventions on opioid reduction. Several trials focus on outcomes of importance to individuals with evidence of LTOT, including pain and functioning, and most are not powered to examine mortality as an outcome, but as the trials are complete, it may be possible to combine their data via meta-analysis to examine mortality.

In reviewing the protocols for the ongoing trials, the committee noted that it avoided the limitations described and largely used pragmatic designs that are relevant to "real-world" practices to manage pain. However, recent studies suggest that opioid tapering may be unwelcome by many individuals on LTOT (Nevedal et al., 2022; Kosakowski et al., 2022; Lovejoy et al., 2017), so the trials may be subject to selection effects related to who is willing to be randomized for opioid tapering.

After reviewing the ongoing and recently completed RCTs, the committee notes that these studies will soon provide critical data relevant to understanding the potential harms and benefits of opioid tapering on a number of outcomes without the major methodological issues associated with retrospective observational studies. However, these trials are likely to be sufficiently powered to examine individual-centric outcomes associated with mortality but not mortality itself.

CONCLUSIONS

The committee did not implement the opioid tapering trial protocol suggested in the 2019 report, considering the following factors in its decision. First, the current statement of task did not direct the committee to examine the effect of opioid tapering on mortality. Second, the committee was aware of studies based on the 2019 report protocol that had been or were being completed and commissioned a review of these and other relevant studies conducted since the 2019 report. Based on the review, the committee determined that the risk of immortal time and selection biases is high and substantially limits the extent to which retrospective observational studies can infer causality between opioid tapering and mortality. Of note, Dr. Erin Krebs and her colleagues applied the 2019 protocol in an unpublished study (see Appendix F) included in the review. It was noted that the study's findings and conclusions were highly sensitive to different study design, statistical modeling, and measurement strategies. In addition, the treatment assignment was based on pharmacy records and as such may not accurately reflect whether a tapering was intended or actually took place. Based on these observations, not available at the time of the 2019 report, the committee concludes that additional efforts to implement such a study is unlikely to yield more definitive results and, for these reasons, the committee chose not to implement the tapering trial suggested in the 2019 report. The committee focused the main report to reflect findings from the analyses addressing the statement of task.

The committee notes that several RCTs will soon produce results and add new knowledge for specific circumstances, including individual-initiated opioid tapering. These studies are subject to bias, most notably selection of who is willing to be randomized in clinical trials. They are not powered to provide information on tapering and all-cause or suicide mortality; however, they may offer an opportunity, once complete, to combine their data via meta-analysis to examine mortality as an outcome.

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TABLE E-2 Randomized Controlled Trial Studies Identified From Search of NIH RePORTER, ClinicalTrials.gov, and PCORI Portfolio

No.	Project Period	Source	Title	Project Summary
1	9/24/2019–5/31/2023	NIH RePORTER	Pain Reduction and Opioid Medication Safety in ESRD (PROMISE) study	**Interventions:** Randomization to two separate 9-month evidence-based interventions: (1) opioid tapering management, and (2) behavioral pain management. The control condition not assigned to either intervention will receive usual care and have the option to receive Acceptance and Commitment Therapy after 12 months. **Outcomes:** Reduction in opioid use (primary outcome) and improving pain severity (secondary outcome).
2	9/24/2019–5/31/2024	NIH RePORTER	Video-Telecare Collaborative Pain Management to Improve Function and Reduce Opioid Risk in Patients with End Stage Renal Disease Receiving Hemodialysis	**Interventions:** Pragmatic randomized sequential, multiple assignment randomized trial. Individuals randomized to (1) Collaborative Opioid Reassessment Program–supported taper with, and (2) without buprenorphine rotation. **Outcomes:** 6-month composite outcome of LTOT dose reduction and pain response.
3	8/1/2022–6/30/2027	NIH RePORTER	Evaluating a Mechanistically Supported Pharmacotherapy to Treat Acute and Protracted Opioid Withdrawal	**Interventions:** Placebo-controlled double-blind randomized controlled trials (RCT). Individuals randomized to (1) Buspirone during both residential and outpatient phases, (2) Buspirone during the residential phase and placebo during the outpatient phase, and (3) Placebo during both the residential and outpatient phases. **Outcomes:** Opioid withdrawal severity, craving severity, and anxiety
4	8/15/2023–7/31/2026	NIH RePORTER	Optimizing Patient-Centered Opioid Tapering with Mindfulness-Oriented Recovery Enhancement (MORE)	**Interventions:** Hybrid 2 implementation-effectiveness RCT of MORE as delivered via an economically sustainable, insurance-reimbursable group medical visit (key implementation strategy) as an adjunct to an individual-centered opioid tapering protocol that leverages individual agency and therapeutic expectancy. **Outcomes:** reduction in opioid dosing and opioid-related harms.
5	8/15/2023–7/31/2026	NIH RePORTER	Sequential Trial of Adding Buprenorphine, Cognitive Behavioral Treatment, and Transcranial Magnetic Stimulation to Improve Outcomes of Long-Term Opioid Therapy for Chronic Pain	**Interventions:** Individuals will be randomized to one of the following treatment arms: (1) Drug: buprenorphine patch, (2) Drug: placebo, (3) Device: transcranial magnetic stimulation, or (4) Device: sham transcranial magnetic stimulation.

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TABLE E-2 Continued

No.	Project Period	Source	Title	Project Summary
6	12/30/2025 (Estimated)	CTG	Tapering From Long-Term Opioid Therapy in Chronic Pain Population. Randomized Controlled Trial With 12 Months Follow-Up	**Interventions:** Individuals with long-term non-malignant pain were randomly allocated to (1) Start tapering immediately: tapering with weekly follow-up by nurse at the beginning; in an outpatient setting; follow-up with doctor after 4 months, or (2) Control group: returned to usual care and commenced tapering of opioids 4 months later. **Outcomes:** Opioid consumption (time frame: 12 months and 4 months).
7	3/22/2018–8/31/2023	CTG	Developing and Pilot Testing an Opioid Tapering Protocol	**Interventions:** Individuals on moderate to high-dose chronic opioid pharmacotherapy for whom providers recommend tapering will be randomized to (1) Opioid tapering protocolized intervention, or (2) Usual care. **Outcomes:** Change in opioid dose over 6 months (time frame: up to 6 months).
8	7/1/2022–2024-07 (Estimated)	CTG	Slow Opioid Tapering Pilot Study of Patients Using Chronic Opioid Therapy	**Interventions:** Individuals randomized to the following: (1) Slow tapering of chronic opioid pharmacotherapy: those on a stable dose for at least 6 months will have their doses slowly and gradually reduced every 4 weeks, or (2) Continued opioid pharmacotherapy: those on a stable dose for at least 6 months will stay on the same dose for the entire 12-month duration of the study. **Outcomes:** Changes in measures of quality of life; change in measures of depression and anxiety.
9	2016-05–2022-11	CTG	Discontinuation From Chronic Opioid Therapy for Pain Using a Buprenorphine Taper	**Interventions**: (1) Drug: buprenorphine initiation—Phase I, (2) Drug: gabapentin + buprenorphine—Phase II, (3) Drug: placebo + buprenorphine—Phase II, (4) Drug: buprenorphine taper—Phase II. **Outcomes:** Percentage of individuals who tolerate buprenorphine initiation (time frame: 8 hours post dose); number of participants achieving opioid cessation (time frame: 8 weeks after stabilization at Week 10); number of participants achieving opioid cessation post-taper: 1 month (time frame: 1 month post-taper).

continued

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TABLE E-2 Continued

No.	Project Period	Source	Title	Project Summary
10	2024-02–2028-07 (Estimated)	CTG	Comprehensive Analgesic, Recovery, and Education Support for Spine Surgery Trial	**Interventions:** Individuals with preoperative long term opioid use (LTOU) undergoing spine surgery randomized to: (1) MI-opioid taper and tizanidine, (2) MI-opioid taper and placebo, or (3) Enhanced usual care. **Outcomes:** Time to baseline opioid use (time frame: up to 1 year after surgery).
11	2016–11/1/2023	PCORI Portfolio	Comparing Ways to Help Veterans Manage Chronic Pain	**Interventions:** Two types of chronic pain care for veterans in reducing pain and daily dose of opioids: (1) Integrated pain team. Veterans received care from a team that included a doctor, a mental health therapist, and a rehabilitation therapist or pharmacist. (2) Telecare collaborative management. Veterans received care led by a pharmacist. For those receiving high-dose opioids, the research team also compared offering versus not offering a switch to buprenorphine, a medicine that can treat pain or opioid use disorder. **Key Findings:** After 1 year, veterans who received the two types of care did not differ in overall pain or daily dose of opioids. For veterans receiving high doses, those who were or were not offered buprenorphine did not differ in overall pain or daily dose of opioids. **Outcomes:** Pain response (time frame: 12 months); 50 percent reduction in daily dose (time frame: 12 months).
12	2016–3/1/2024	PCORI Portfolio	Managing Long-Term Low Back Pain to Improve Health and Reduce Reliance on Opioid Medicines: Comparing Mindfulness Meditation and Cognitive Behavioral Therapy—Strategies to Assist with Management of Pain	**Interventions:** Individuals with low back pain taking opioids received one of two interventions: (1) Training in mindfulness meditation, or (2) Training in cognitive behavioral therapy (CBT). **Outcomes:** Opioid use, functioning, and pain at 1 year.
13	2017–3/1/2024	PCORI Portfolio	Comparing Cognitive Behavioral Therapy with Peer-Led Support Groups for Patients with Chronic Pain Who Want to Reduce Opioid Use	**Interventions:** Individuals with chronic pain created a plan with their doctor to slowly reduce their opioid use and received one of the following: (1) Psychologist-led group CBT for chronic pain, (2) Peer-led group sessions on self-managing chronic pain, or (3) Usual care. **Outcomes:** Pain level and opioid use at 1 year.

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TABLE E-2 Continued

No.	Project Period	Source	Title	Project Summary
14	2017–3/1/2025	PCORI Portfolio	Comparing Two Ways to Help Patients Manage Long-Term Non-Cancer Pain	**Setting:** Three health systems in North Carolina and Tennessee. **Interventions:** Individuals with chronic pain taking opioids received one of the following: (1) Physician training on communication and shared decision making, or (2) Individual therapy on knowledge, beliefs, and skills to manage pain. **Outcomes:** Continued opioid use, functioning, pain, and other symptoms at 6, 12, and 18 months.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

ANNEX: EFFECT OF OPIOID TAPERING ON MORTALITY AND OTHER ADVERSE OUTCOMES: A RAPID SYSTEMATIC REVIEW

In November 2023, the National Academies of Sciences, Engineering, and Medicine (National Academies) contracted with the University of Pennsylvania's Penn Medicine Center for Evidence-Based Practice (CEP) to conduct a rapid systematic review to inform the efforts of the Committee on Evaluating the Effects of Opioid and Benzodiazepine Co-Prescribing on All-Cause Mortality in Veterans. The review was completed in April 2024.

Methods

Literature Search

The initial search conducted by the National Academies identified 498 studies of potential interest, which were screened at title, abstract, and full-text levels. To identify additional studies, CEP performed snowball searches by manually reviewing the reference lists of all studies published in 2023 that were selected for inclusion, all systematic reviews published since 2020, and a Cochrane review published in 2017. This approach was selected to efficiently maximize output and limit redundancy. The snowball searches identified 16 additional studies for potential inclusion, which were screened.

Inclusion and Exclusion Criteria

The searches identified studies published in English between 2007 and 2023. Table E-3 lists the reasons for excluding studies.

Outcomes of Interest

The primary outcome of this review was mortality, including all cause, opioid overdose related, and fatal suicide. Secondary outcomes included the following:

- *Behavioral health*: suicidal ideation; suicide attempts; depression; anxiety.
- *Opioid-related morbidity*: opioid overdose; substance use disorder; functional impairment.
- *Health care use*: emergency department (ED) visits; readmissions; outpatient visits.
- *Failure of tapering* as indicated by opioid dose increase.

TABLE E-3 Exclusion Criteria

Category	Exclusion
Publication type	Meeting abstracts Editorials, letters, errata Single case reports Guidelines or reviews
Population	Not U.S. Pediatric Not long-term opioid pharmacotherapy treatment
Intervention or comparison	Did not examine effect of tapering opioid treatment
Outcomes	Did not report adverse events Only reported peripheral outcomes (e.g., withdrawal symptoms, pain or heat sensitivity)

NOTE: Tapering was defined to include the gradual, rapid, or abrupt dosage reduction or discontinuation of prescription opioids.
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Peripheral outcomes of lesser interest were also identified, including measures of pain sensitivity and heat sensitivity. Withdrawal symptoms were not assessed except when included as a component of a composite measure (e.g., some studies evaluated the combined risk of experiencing an opioid overdose, withdrawal symptoms, or other adverse event).

Data Extraction

Table E-4 lists the elements of each study that were described in the summary table.

Risk of Bias Assessment

Each study was assessed for risk of bias using standardized tools developed by Cochrane. RCTs were evaluated with the revised *Cochrane risk-of-bias tool for randomized trials (RoB 2)*. It was updated in 2019 and includes 28 criteria across five domains: (1) randomization, (2) deviation from the intended intervention, (3) missing outcome data, (4) outcome measurement, and (5) selection of results.

Non-randomized studies were evaluated with the *Risk of Bias in Non-Randomized Studies—of Interventions (ROBINS-I)* tool. Developed in 2016, it assesses 32 criteria across seven domains: (1) confounding, (2) participant selection, (3) classification of intervention, (4) deviation from the intended intervention, (5) missing outcome data, (6) outcome measurement, and (7) selection of results.

Additionally, at the suggestion of the committee, CEP evaluated the risk of immortal time bias for studies that reported mortality as an outcome. This was integrated as an additional domain into the Cochrane assessments.

Each domain was given a risk-of-bias assessment, and the individual domain ratings were then combined to yield an overall risk of bias for every study, categorized as low, moderate, serious, or critical. Cochrane characterizes these levels as follows:

- "Low" = is comparable to a well-performed randomized study.
- "Moderate" = provides sound evidence but cannot be considered comparable to a well-performed randomized study.
- "Serious" = has important problems.
- "Critical" = is too problematic to provide useful evidence.

The Appendix tables present detailed information on how to interpret the domain-specific and overall risk-of-bias assessments. The scoring algorithm indicates that if any single domain in a given study is assessed to be at moderate risk, then the overall risk for the study should not be better than moderate, even if all other domains are low. Furthermore, the risk-of-bias tools do not indicate or confirm that the results of a study are actually biased or

TABLE E-4 Study Data

Study characteristics	Title, author, year of publication. Study period/duration.
Population	Total *N* of included population. Veterans or non-veterans. Exclusion criteria.
Methodology	Study design. Data sources. Definition of long-term opioid pharmacotherapy. Definition of tapering.
Results	Description of outcome measures. Concise summary of results.

SOURCE: Penn Medicine CEP, consultants to the committee.

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that the results are, or are not, valid and reliable. Rather, the tools identify potential sources of bias and indicate the likelihood that various types of bias might have affected a study.

Results

The searches identified 514 studies for screening, and 31 were selected for inclusion. Figure E-1 summarizes the screening process.

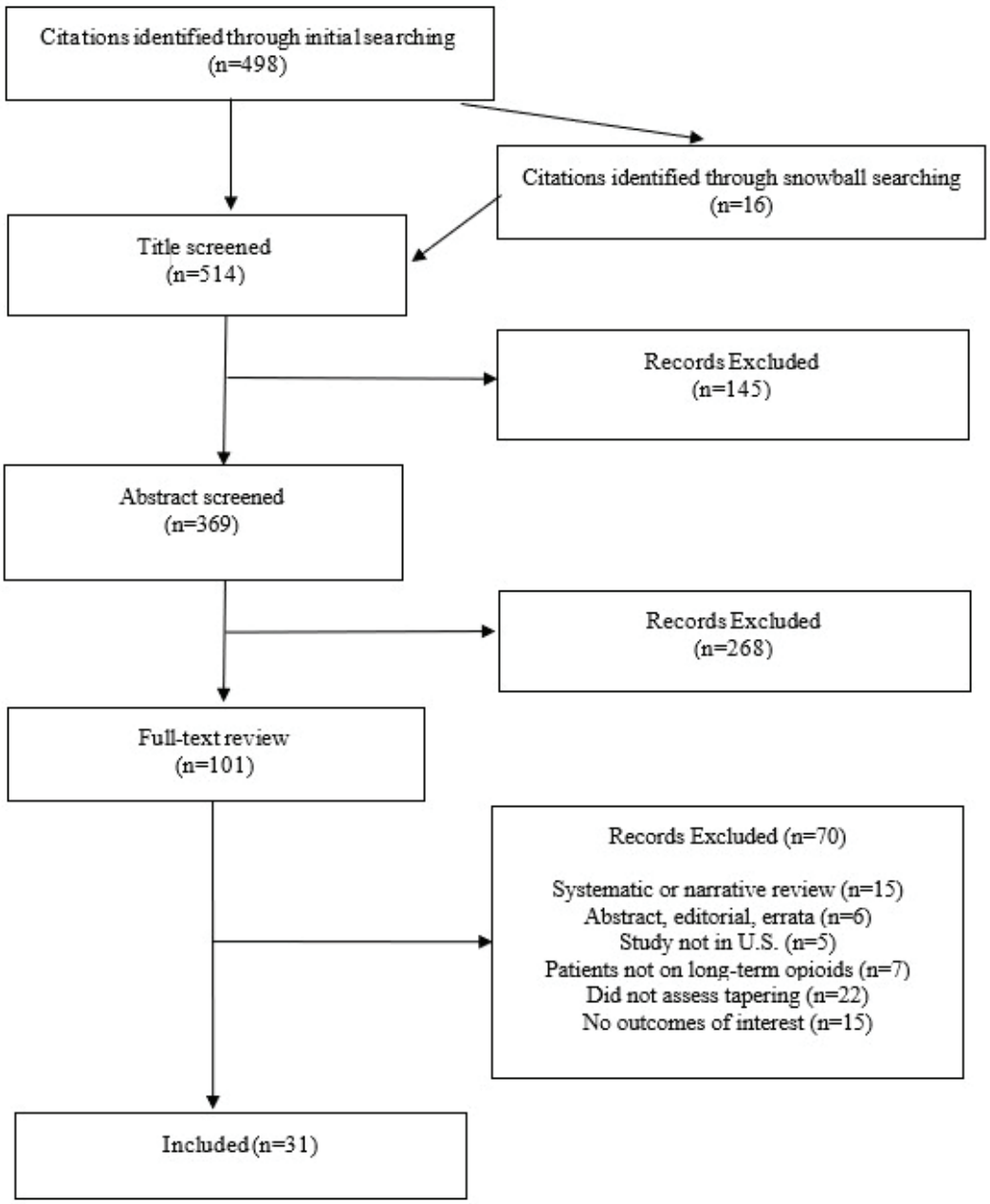

FIGURE E-1 Study flow diagram.
SOURCE: Penn Medicine CEP, consultants to the committee.

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Study Characteristics

Thirty-one studies of opioid tapering in U.S. adults were included. Six studies focused exclusively on U.S. veterans; the others included a broader population. Eight studies reported data on mortality; four of those and four other studies reported episodes of nonfatal suicide and/or opioid overdose. Seven studies described ED visits or hospitalizations.

Nineteen studies focused on opioid dosage reduction; 12 studies examined the complete discontinuation of opioid treatment. In 17 studies, a minimum daily dose of opioids was used as an eligibility criterion. Eight of these studies used a threshold of at least 50 morphine milligram equivalents (MME)/per day. Two studies used lower thresholds (20 and 25); the others used higher baselines, 90–300.

All but one study was published since 2017, and one-third of the studies are from 2022 and 2023. One study that used data collected during 2016 is unpublished. Figure E-2 summarizes the distribution by year.

Only one RCT was found, while two-thirds of the studies used retrospective cohort designs. Table E-5 summarizes the study designs.

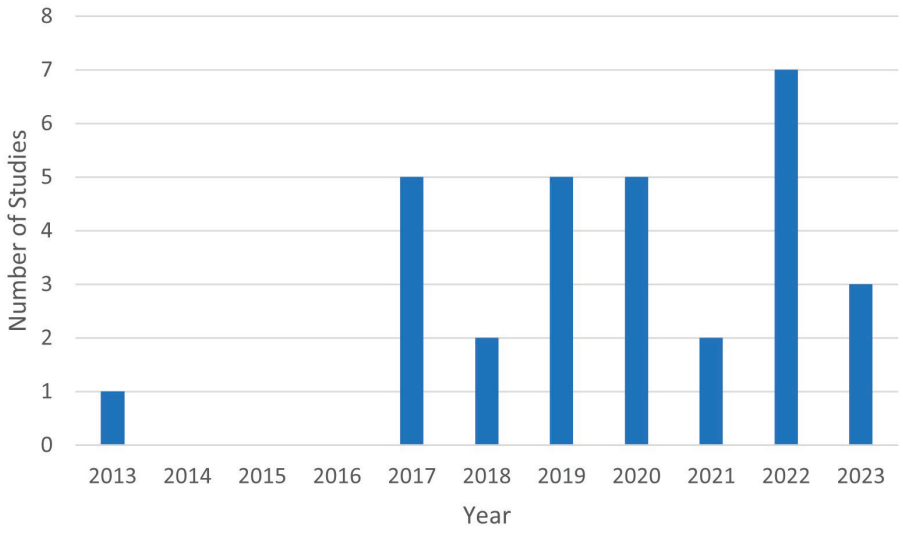

FIGURE E-2 Year of publication of included studies.
SOURCE: Penn Medicine CEP, consultants to the committee.

TABLE E-5 Study Design

Study Design	N
Randomized Controlled Trial	1
Prospective cohort	1
Retrospective cohort	22
Chart review	3
Case control	3
Survey	1

SOURCE: Penn Medicine CEP, consultants to the committee.

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When risk of bias was assessed, 20 studies were rated as moderate, 10 studies as serious, and one as critical. For the 29 non-randomized studies, the primary concerns related to the potential for confounding of results, patients deviating from the intended tapering pathway, and missing data. Immortal time bias was evaluated for the 11 studies that reported mortality or associated outcomes (such as overdose or suicidal ideation). Five studies were assessed as low risk for immortal time bias, three as moderate, two as serious, and one (Oliva et al., 2020) as critical.

Outcomes

Mortality

The eight studies examining mortality presented heterogeneous results that may not be easily reconciled. Three studies reported all-cause mortality, and two found that tapering was not associated with an effect, while one study reported an increase in deaths in a population with a large rather than small dose reduction. Two studies reported suicide mortality, with one finding an increased risk associated with discontinuation and the other no effect. Three studies examined a combined metric for fatal and nonfatal overdoses; two reported that tapering was associated with increased risk of overdose, but the third study found no effect. Finally, two studies used a composite measure of suicide mortality and overdose, and both found that tapering was associated with higher risk. Only two of these studies focused on populations of veterans: the unpublished Krebs study and the large Oliva and colleagues (2020) study that was evaluated as having a critical risk of bias. Table E-6 presents key findings from these studies, excerpted from the full data summary tables.

Six studies were assessed as moderate risk of bias, due primarily to the possibility of confounding variables contributing to the outcomes and some concern about missing data or immortal time bias in several studies. One study was assessed at serious risk of bias because of substantial concerns about immortal time bias and patients who deviated from the intended tapering intervention. One study was rated as having a critical risk of bias because immortal time bias may have had a significant impact on the results; this study was also assessed as serious risk for how interventions were classified and outcomes measured.

Nonfatal Major Adverse Outcomes

Eight studies, including seven at moderate risk of bias due mainly to potential confounding, reported data on a variety of critical but nonfatal adverse events. Two studies found that tapering was associated with higher risk for overdose. One study, at serious risk of bias due to concerns about immortal time bias, reported that 9 percent of veterans experienced suicidal ideation following opioid discontinuation. Three studies found no significant association between tapering and subsequent opioid use or misuse, but two studies did find that patients who discontinued opioids were more likely to use heroin. Finally, two studies found an association between tapering and mental health crises. Table E-7 presents key findings from these studies.

Health Care Utilization

Several studies examined the effects of tapering on the use of ED, hospital, and primary care services. Two studies at moderate risk of bias reported that tapering was associated with a higher risk of ED use and hospitalization, while one small study at serious risk of bias found no difference in ED use after opioid discontinuation. Additionally, two studies found that tapering was associated with fewer primary care visits. The potential for confounding again accounts for almost all the concern related to risk of bias. Table E-8 summarizes these studies.

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TABLE E-6 Mortality Results

Study and Population	Results	Overall Risk of Bias
	All-Cause Mortality	
Binswanger et al., 2022 *N* = 3,913 Non-veterans	Decreasing dose trajectory, compared to stable trajectories, was not associated with all-cause mortality. aHR: 1.28; 95% CI: 0.87–1.86. High-dose increasing trajectory was positively associated with mortality. aHR: 2.19; 95% CI: 1.44–3.32.	Moderate
James et al., 2019 *N* = 572 Non-veterans	Discontinuation was not associated with a significant risk for all-cause mortality. HR: 1.35; 95% CI: 0.92–1.98; *p* = 0.122.	Moderate
Krebs et al., unpublished *N* = 207,204 Veterans	No difference was reported in risk of all-cause mortality between small dose reduction and control groups. HR: 1.01; 95% CI: 0.98–1.04. Large dose reduction group had a small, statistically significant increase in all-cause mortality risk compared to the control group. HR: 1.23; 95% CI: 1.20–1.27.	Moderate
	Suicide Mortality	
Hallvik et al., 2022 *N* = 14,596 Non-veterans	Discontinuation was associated with increased risk of suicide mortality compared to stable or increasing dose: Abrupt discontinuation patients aHR: 3.63; 95% CI: 1.42–9.25. Reduction and discontinuation aHR: 4.47; 95% CI: 1.68–11.88. Dose reduction without discontinuation aHR: 1.29; 95% CI: 0.48–3.45.	Moderate
Krebs et al., unpublished *N* = 207,204 Veterans	No difference in risk of suicide mortality was reported for small dose reduction group versus control group. HR: 1.09; 95% CI: 0.89–1.35. No difference in risk of suicide mortality was reported for large dose reduction group versus control group. HR: 1.01; 95% CI: 0.77–1.33. Among patients who died during 1-year follow-up, there was no difference in risk of suicide mortality (as opposed to other cause of death) for either treatment comparison.	Moderate
	Overdoses, Fatal and Nonfatal	
DiPrete et al., 2022 *N* = 19,443 Non-veterans	Rapid reduction or discontinuation was associated with higher risk of fatal and nonfatal overdoses compared with gradual reduction after the first year. Year 1 HR: 1.43; 95% CI: 0.94–2.18. Years 2–4 HR: 1.95; 95% CI: 1.31–2.90.	Moderate
James et al., 2019 *N* = 572 Non-veterans	Discontinuation was associated with risk for overdose death. HR: 2.94; 95% CI: 1.01–8.61; *p* = 0.049.	Moderate
Von Korff et al., 2019 *N* = 31,142 Non-veterans	No difference was found in risk of overdose between tapering and control groups. RR: 0.76; 95% CI: 0.50–1.13.	Serious
	Overdose or Suicide	
Larochelle et al., 2022 *N* = 199,836 Non-veterans	Tapering was associated with increased risk of mortality from opioid overdose or suicide compared to stable dosage. Taper RR: 1.15; 95% CI: 1.04–1.27. Abrupt discontinuation RR: 1.34; 95% CI: 0.97–1.79.	Moderate
Oliva et al., 2020 *N* = 1,394,102 Veterans	Stopping opioid treatment was associated with increased risk of mortality from overdose or suicide. Stopping after <=30 days of opioid use HR: 1.67; 31–90 days of opioid use HR: 2.80; 91–400 days of opioid use HR: 3.95; >400 days of opioid use HR: 6.77.	Critical

NOTES: aHR = adjusted hazard ratio; CI = confidence interval; HR = hazard ratio; RR = risk ratio.
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TABLE E-7 Nonfatal Adverse Outcomes

Study and Population	Results	Overall Risk of Bias
	Nonfatal Overdose	
Fenton et al., 2022 *N* = 19,377 Non-veterans	Tapering was associated with increased risk of nonfatal overdose or withdrawal symptoms compared to the pre-taper period. Overdose or withdrawal aIRR: 1.57; 95% CI: 1.42–1.74.	Moderate
Agnoli et al., 2021 *N* = 113,618 Non-veterans	Tapering was associated with increased risk of nonfatal overdose compared with non-tapering. Nonfatal overdose aIRR: 1.28; 95% CI: 1.15–1.43.	Moderate
	Suicidal Ideation	
Demidenko et al., 2017 *N* = 509 Veterans	After discontinuation, 47 patients (9%) had suicidal ideation, and 12 patients (2%) had suicidal self-directed violence.	Serious
	Opioid Use	
Sullivan et al., 2017 *N* = 35 Non-veterans	Tapering was not associated with risk of opioid misuse. Opioid misuse (adjusted mean difference):0.06; 95% CI: -0.45–0.57; $p = 0.81$.	Moderate
Von Korff et al., 2017 *N* = 1,588 Non-veterans	Tapering was not associated with risk of opioid use disorder (OUD). Prevalence of OUD in tapering group: 21.5%; 95% CI: 18.9–24.4. Prevalence in control group: 23.9%; 95% CI: 20.5–27.6. aRR: 1.08; 95% CI: 0.89–1.32.	Moderate
Huffman et al., 2013 *N* = 120 Non-veterans	One year after discontinuation, 22.5% of patients had resumed opioid use. Patients who had previously been diagnosed with opioid abuse were no more likely than other patients to have resumed use.	Moderate
	Heroin Use	
Binswanger et al., 2020 *N* = 22,962 Non-veterans	Compared with no opioid discontinuations, one discontinuation was associated with heroin use. mOR: 2.54; 95% CI: 1.33–4.84. 2 discontinuations (mOR: 2.07; 95% CI: 0.93–4.58) and ≥3 discontinuations (mOR: 1.82; 95% CI: 0.79–4.20) were not significantly associated with heroin use. In a multivariable model, case patients were more than twice as likely to have been discontinued from opioids than control patients. mOR: 2.19; 95% CI: 1.27–3.78.	Moderate
Coffin et al., 2020 *N* = 602 Non-veterans	Participants discontinued from opioids were more likely to use heroin. aOR: 1.57; 95% CI: 1.25–1.97.	Moderate
	Mental Health Crisis	
Fenton et al., 2022 *N* = 19,377 Non-veterans	Tapering was associated with increased risk of mental health crisis. aIRR: 1.52; 95% CI: 1.35–1.71.	Moderate
Agnoli et al., 2021 *N* = 113,618 Non-veterans	Tapering was associated with increased risk of mental health crisis. aIRR: 1.74; 95% CI: 1.50–2.01.	Moderate

NOTES: aIRR = adjusted incidence rate ratio; aOR = adjusted odds ratio; aRR = adjusted risk ratio; CI = confidence interval; mOR = matched odds ratio.
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TABLE E-8 Health Care Utilization

Study and Population	Results	Overall Risk of Bias
	ED Visits	
Magnan et al., 2023 *N* = 113,604 Non-veterans	Tapering was associated with increased risk of emergency department (ED) use. aIRR: 1.19; 95% CI: 1.16–1.21.	Moderate
Mazurenko et al., 2023 *N* = 9,633 Non-veterans	Tapering was associated with increased risk of ED use. 50% tapering OR: 1.75; 95% CI: 1.48–2.06; $p < 0.001$. 30% tapering OR: 1.73; 95% CI: 1.50–1.98; $p < 0.001$.	Moderate
Husain et al., 2019 *N* = 125 Non-veterans	Discontinuation was not associated with statistically significant change in ED use for pain: 15% in discontinued patients versus 5% in control group; $p = 0.10$.	Serious
Mark et al., 2019 *N* = 494 Non-veterans	45% of discontinued patients had an ED visit.	Moderate
	Hospitalizations	
Magnan et al., 2023 *N* = 113,604 Non-veterans	Tapering was associated with increased risk of hospitalization. aIRR: 1.16; 95% CI: 1.12–1.20.	Moderate
Mazurenko et al., 2023 *N* = 9, et al., 633 Non-veterans	Tapering was associated with increased risk of hospitalization. 50% tapering OR: 1.67; 95% CI: 1.30–2.15; $p < 0.001$. 30% tapering OR: 1.39; 95% CI: 1.13–1.70; $p < 0.001$.	Moderate
Mark and Parish, 2019 *N* = 494 Non-veterans	3% of discontinued patients had a hospitalization.	Moderate
	Primary Care Visits	
Magnan et al., 2023 *N* = 113,604 Non-veterans	Tapering was associated with fewer primary care visits. aIRR: 0.95; 95% CI: 0.94–0.96.	Moderate
Husain et al., 2019 *N* = 125 Non-veterans	Discontinuation was associated with fewer primary care visits: 65% in discontinued patients versus 88% in control group; $p < 0.01$.	Serious

NOTES: aIRR = adjusted incidence rate ratio; CI = confidence interval; ED = emergency department; OR = odds ratio.
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Conclusions

The evidence base is complex and does not point to clear, consistent conclusions. Recent studies suggest that tapering may not be associated with all-cause mortality but might be associated with higher risk of death from overdose or suicide. Tapering was also associated with increased risk of nonfatal overdose, heroin use, or mental health crises in five studies, while three different studies found that it did not lead to opioid misuse. ED visits and hospitalizations appeared to increase when patients tapered opioid use, while primary care visits decreased.

In addition to the difficulty of reconciling these results, synthesizing the findings is challenging due to heterogeneous populations and limitations of the study designs. Only two of eight studies that reported mortality outcomes focused on populations of veterans, while just six of the overall set of 31 studies were specific to veterans. Tapering interventions varied widely, including 19 studies that reduced opioid dosage and 12 studies that entirely discontinued use, while the eight studies that reported mortality were evenly divided between dose reduction and discontinuation. Variability was also seen in how gradually or abruptly changes were initiated, with heterogeneity in how patients on LTOT were defined or identified.

The included studies also have inherent limitations. Most of them relied on large administrative and/or clinical databases that inherently have missing, inaccurate, or incomplete data. Additionally, opioid tapering can be clinically complex, and many patients may deviate from an intended regimen in various ways. Only one RCT was identified, while two-thirds of the studies used retrospective cohort designs. Many of these observational studies were assessed to be at moderate or higher risk of bias because, even after adjusting for multiple factors, it is unlikely that they could adequately account for all substantive sources of confounding, particularly for outcomes such as mortality, overdose, or ED use. Also, as noted, the risk-of-bias assessments indicate the broad likelihood that a given study might be biased in the specified domains but do not confirm that the results are in fact biased or invalid. For outcomes where the study findings are consistent and the risk of bias for the relevant studies is moderate to low, the results are likely to be more trustworthy. Where the findings are inconsistent and/or risk of bias is serious or critical, examining the specific risk of bias associated with each study may be one tool to address the challenges of interpreting the evidence base.

Finally, the evidence base reveals important evidence gaps. Only six studies since 2007 were identified that examined tapering in a population of veterans. Just three studies assessed all-cause mortality, including one that is unpublished. And only one RCT and one prospective cohort study were found, demonstrating a need for more robust research.

Risk of Bias Assessment

Tables E-9 and E-10 describe how to interpret the ROBINS-I risk-of-bias domains and overall assessment. These tables are excerpted from *The Risk of Bias in Non-Randomized Studies—of Interventions (ROBINS-I) assessment tool*, available at the Current version of ROBINS-I. The tool is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

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TABLE E-9 Interpreting Risk of Bias Assessment by Domain for ROBINS-I

Judgment	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	No confounding expected.	(i) All participants who would have been eligible for the target trial were included in the study; and (ii) For each participant, start of follow-up and start of intervention coincided.	(i) Intervention status is well defined; and (ii) Intervention definition is based solely on information collected at the time of intervention.	The important co-interventions were balanced across intervention groups, and there were no deviations from the intended interventions (in terms of implementation or adherence) that were likely to impact on the outcome	(i) Data were reasonably complete; or (ii) Proportions of and reasons for missing participants were similar across intervention groups; or (iii) The analysis addressed missing data and is likely to have removed any risk of bias.	(i) The methods of outcome assessment were comparable across intervention groups; and (ii) The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is objective) or the outcome assessors were unaware of the intervention received by study participants; and (iii) Any error in measuring the outcome is unrelated to intervention status.	There is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub-cohorts.
Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)	(i) Confounding expected, all known important confounding domains appropriately measured and controlled for; and (ii) Reliability and validity of measurement of important domains were sufficient, such that serious residual confounding is not expected.	(i) Selection into the study may have been related to intervention and outcome; and The authors used appropriate methods to adjust for the selection bias; or (ii) Start of follow-up and start of intervention do not coincide for all participants; and (a) the proportion of participants for which this was the case was too low to induce important bias; or (b) the authors used appropriate methods to adjust for the selection bias; or (c) the review	(i) Intervention status is well defined; and (ii) Some aspects of the assignments of intervention status were determined retrospectively.	(i) There were deviations from intended intervention, but their impact on the outcome is expected to be slight. or (ii) The important co-interventions were not balanced across intervention groups, or there were deviations from the intended interventions (in terms of implementation and/or adherence) that were likely to impact on the outcome; and The analysis was appropriate to estimate the effect of starting and adhering to intervention, allowing for deviations (in terms of implementation, adherence	(i) Proportions of and reasons for missing participants differ slightly across intervention groups; and (ii) The analysis is unlikely to have removed the risk of bias arising from the missing data.	(i) The methods of outcome assessment were comparable across intervention groups; and (ii) The outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and (iii) Any error in measuring the outcome is only minimally related to intervention status.	(i) The outcome measurements and analyses are consistent with an a priori plan; or are clearly defined and both internally and externally consistent; and (ii) There is no indication of selection of the reported analysis from among multiple analyses; and (iii) There is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.

continued

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TABLE E-9 Continued

Judgment	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
		authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time.	and co-intervention) that were likely to impact on the outcome.				
Serious risk of bias (the study has some important problems)	(i) At least one known important domain was not appropriately measured, or not controlled for; or (ii) Reliability or validity of measurement of an important domain was low enough that serious residual confounding is expected.	(i) Selection into the study was related (but not very strongly) to intervention and outcome; and This could not be adjusted for in analyses; or (ii) Start of follow-up and start of intervention do not coincide; and A potentially important amount of follow-up time is missing from analyses; and the rate ratio is not constant over time.	(i) Intervention status is not well defined; or (ii) Major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.	(i) The important co-interventions were not balanced across intervention groups, or there were deviations from the intended interventions (in terms of implementation and/or adherence) that were likely to impact on the outcome; and (ii) The analysis was not appropriate to estimate the effect of starting and adhering to intervention, allowing for deviations (in terms of implementation, adherence and co-intervention) that were likely to impact on the outcome.	(i) Proportions of missing participants differ substantially across interventions; or Reasons for missingness differ substantially across interventions; and (ii) The analysis is unlikely to have removed the risk of bias arising from the missing data; or Missing data were addressed inappropriately in the analysis; or the nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.	(i) The methods of outcome assessment were not comparable across intervention groups; or (ii) The outcome measure was subjective (i.e., vulnerable to influence by knowledge of the intervention received by study participants); and the outcome was assessed by assessors aware of the intervention received by study participants; or (iii) Error in measuring the outcome was related to intervention status.	(i) Outcomes are defined in different ways in the methods and results sections, or in different publications of the study; or (ii) There is a high risk of selective reporting from among multiple analyses; or (iii) The cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results.

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Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)	(i) Confounding inherently not controllable or (ii) The use of negative controls strongly suggests unmeasured confounding.	(i) Selection into the study was very strongly related to intervention and outcome; and This could not be adjusted for in analyses; or (ii) A substantial amount of follow-up time is likely to be missing from analyses; and the rate ratio is not constant over time.	(Unusual) An extremely high amount of misclassification of intervention status (e.g., because of unusually strong recall biases).	(i) There were substantial imbalances in important co-interventions across intervention groups, or there were substantial deviations from the intended interventions (in terms of implementation and/or adherence) that were likely to impact on the outcome; and (ii) The analysis was not appropriate to estimate the effect of starting and adhering to intervention, allowing for deviations (in terms of implementation, adherence and co-intervention) that were likely to impact on the outcome.	(i) (Unusual) There were critical differences between interventions in participants with missing data; and (ii) Missing data were not, or could not, be addressed through appropriate analysis.	The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups.	(i) There is evidence or strong suspicion of selective reporting of results; and (ii) The unreported results are likely to be substantially different from the reported results.
No information on which to base a judgment about risk of bias for this domain.	No information on whether confounding might be present.	No information is reported about selection of participants into the study or whether start of follow-up and start of intervention coincide.	No definition of the intervention or no explanation of the source of information about intervention status is reported.	No information is reported on whether there is deviation from the intended intervention.	No information is reported about missing data or the potential for data to be missing.	No information is reported about the methods of outcome assessment.	There is too little information to make a judgment (for example, if only an abstract is available for the study).

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TABLE E-10 Overall Risk-of-Bias Assessment for ROBINS-I

Judgment	Within Each Domain	Across Domains	Criterion
Low risk of bias	The study is comparable to a well-performed randomized trial with regard to this domain	The study is comparable to a well-performed randomized trial	The study is judged to be at **low risk of bias for all domains**
Moderate risk of bias	The study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial	The study provides sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial	The study is judged to be at **low or moderate risk of bias for all domains**
Serious risk of bias	The study has some important problems in this domain	The study has some important problems	The study is judged to be at **serious risk of bias in at least one domain**, but not at critical risk of bias in any domain
Critical risk of bias	The study is too problematic in this domain to provide any useful evidence on the effects of intervention	The study is too problematic to provide any useful evidence and should not be included in any synthesis	The study is judged to be at **critical risk of bias in at least one domain**.
No information	No information on which to base a judgment about risk of bias for this domain	No information on which to base a judgment about risk of bias	There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias

SOURCE: Penn Medicine CEP, consultants to the committee.

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Report of Preliminary Results: Opioid Dose Reduction Trial Emulation

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ABSTRACT

Introduction: We conducted an observational study designed to emulate a randomized parallel-arm trial using an existing cohort of Department of Veterans Administration (VA) patients who received long-term opioid therapy (LTOT) in 2016. Aims were to 1) compare effects of each of two active opioid dose reduction strategies (small reduction, large reduction) vs. no dose reduction control on all-cause mortality (primary outcome) and suicide mortality (secondary outcome) in VA primary care patients receiving LTOT and 2) to assess for varying treatment effects in subgroups defined by presence or absence of concomitant benzodiazepine treatment at baseline.

Methods: Eligibility was determined in 2016. Patients who had received opioids for at least 6 months and had a baseline daily dose of at least 20 morphine-equivalent (ME) mg were eligible for inclusion. Active treatment strategies were 1) small dose reduction (decrease of 15% to <50% in daily dosage from baseline) and 2) large dose reduction (decrease of 50% or more from baseline); the control group was no dose reduction (<15% decrease from baseline). Treatment group assignment was determined during a six-month treatment implementation period and outcomes were assessed over 12 months (including the implementation period). Randomization was emulated by cloning of patients. Inverse-probability-of-censoring weights (IPCW) were created to address selection bias introduced by censoring of clones. Weighted Cox proportional hazards models were used to separately compare small dose reduction vs. control and large dose reduction vs. control. Analyses were stratified by baseline opioid daily dose category and presence or absence of benzodiazepine treatment at baseline.

Results: Over 12 months, 9,646 (4.7%) patients died of all causes, including 208 who died of suicide. Overall, there was no difference in risk of all-cause mortality between small reduction and control groups (HR 1.01, 95% CI 0.98, 1.04). The large dose reduction group had a small, statistically significant increase in all-cause mortality risk compared to the control group (HR 1.23; 95% CI 1.20, 1.27). Results for both small reduction vs. control and large reduction vs. control were similar among patients with and without concomitant benzodiazepine treatment at baseline. There was no difference in risk of suicide mortality for small reduction vs. control (HR 1.09, 95% CI 0.89, 1.35) or large reduction vs. control (HR 1.01, 95% CI 0.77, 1.33). Among patients who died during one-year follow-up, there was no difference in risk of suicide death (as opposed to other cause of death) for either treatment comparison.

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Discussion: This study has several important limitations. First, results may be dependent on design decisions such as exposure definitions and time windows. The large dose reduction group in particular was heterogeneous and likely included patients with unplanned gaps in opioid dispensing, as well as those with planned dose reduction or discontinuation. Second, the trial emulation approach does not eliminate bias caused by unmeasured confounding. Factors such as opioid misuse or diversion are important confounders that are not adequately captured in data. Third, we had limited power to detect differences in suicide.

Conclusions: Results should be considered preliminary

INTRODUCTION

Long-term opioid therapy (LTOT) is associated with serious harms, including include death due to unintentional overdose and suicide, as well as all-cause and out-of-hospital mortality. Studies suggest harms increase with longer duration of therapy, higher dosages, and concomitant benzodiazepine use. Following recognition of a U.S. opioid crisis defined by epidemic levels of opioid-overdose deaths, numerous policy and practice initiatives have encouraged opioid dose reduction or discontinuation for patients receiving LTOT. One goal of these initiatives is to reduce opioid-related mortality. At the same time, clinical concerns have been raised about potential negative consequences of opioid dose reduction, especially aggressive or abrupt reductions that could cause opioid withdrawal or psychiatric destabilization. In theory, any mortality benefits (reduction in deaths) due to opioid dose reduction would accrue gradually over time, whereas risks (increase in deaths) would manifest early. A substantial early increase in risk of death could preclude future benefits. Using an approach recommended by a National Academies of Sciences, Engineering, and Medicine committee, this study aimed to evaluate effects of opioid dose reduction strategies on all-cause mortality and suicide mortality among VA patients receiving LTOT with and without concomitant benzodiazepine treatment (NASEM, 2019).

TRIAL EMULATION DESIGN

This observational study was designed to emulate a parallel-arm randomized controlled trial (the "target trial") to compare effects of each of two active opioid dose reduction strategies (small reduction, large reduction) vs. control (no dose reduction) on mortality in patients treated with LTOT for chronic pain. The target trial has a pragmatic approach to implementation of the active interventions, in which opioid prescribers are instructed to work with patients to implement the assigned dose reduction strategy within 6 months. Table F-1 shows design features of the target trial and observational trial emulation study.

ELIGIBILITY

This study used data from the existing Effects of Prescription Opioid Changes in Veterans (EPOCH) population cohort of VA primary care patients on current long-term opioid therapy for chronic pain. (Krebs et al., 2020) Eligibility for the EPOCH cohort was determined using seven data extractions (February 2016 and monthly from June to November 2016) from the VA Corporate Data Warehouse (CDW). EPOCH population cohort eligibility criteria are described in Annex 1. Figure F-1 shows how patients were selected from the EPOCH cohort for this present study.

- Opioid prescriptions were determined from VA outpatient pharmacy dispensing data. Opioid dosage was standardized by calculating morphine-equivalent (ME) mg using CDC-recommended conversion factors (Annex 2). Average daily doses were calculated within 60-day windows to provide stable estimates in the presence of such factors as overlapping prescriptions and variable dispensing dates, while allowing for detection of dosage changes (Annex 3). Baseline opioid daily dosage was calculated as the total dosage (sum of ME mg for all opioids dispensed in the 60 days before and including the index date prescription) divided by the number of days from the first opioid dispensed in the window to the index prescription's

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TABLE F-1 Target Trial and Observational Trial Emulation Design Teatures

	Target trial design	Observational trial emulation design
Eligibility	Inclusion criteria: VA primary care patients receiving long-term opioid therapy for chronic pain with current daily dose of ≥20 ME mg. Exclusion criteria: Opioids for end of life care, active cancer, or opioid use disorder; life expectancy < one year; moderate-severe cognitive impairment; nursing home residence.	Inclusion criteria: Same Exclusion criteria: Opioid use disorder treatment, dementia diagnosis or treatment, cancer treatment, end-of-life care, or adult day care in the past 12 months; nursing home residence.
Opioid treatment strategies	Small dose reduction (decrease of 15% to <50% from baseline) Large dose reduction (decrease of 50% or more from baseline) Control (no dose reduction)	Small dose reduction (decrease of 15% to <50% from baseline) Large dose reduction (decrease of 50% or more from baseline) Control (<15% decrease from baseline)
Treatment assignment	Blocked randomization with blocks defined by baseline daily dose category.	Randomization emulated by cloning of patients. Analysis stratified by baseline daily dose category.
Treatment implementation	Six-month period for individualized implementation of target dose reduction	Six-month treatment implementation period
Outcome	Time to all-cause mortality (primary); time to suicide mortality (secondary)	Same
Follow up	Follow up for one year following randomization date	Follow up for one year following index date
Contrast	Intention-to-treat effect and per-protocol effect of each dose reduction strategy vs. control	Per-protocol effect of each dose reduction strategy vs. control

end date (i.e., dispensing date + days' supply). Average daily dosage at successive monthly time points after the index date was calculated similarly; each month, the total dosage for the prior 60 days was divided by the number of days from the first dispensing date to the end date of the last prescription dispensed in the window. If no opioids were dispensed in the 60-day window, the daily dosage was considered to be zero. Baseline opioid daily dosage was categorized using conventional cutoffs into three groups: 20 to <50 mg, 50 to <100 mg, ≥100 mg. Analyses treated opioid daily dosage as a continuous variable in 10 ME mg increments.

- Benzodiazepine treatment at baseline was defined as any benzodiazepine prescription dispensed in the 60 days before and including the index date.
- All-cause mortality and survival were evaluated using the CDW patient table and vital status file. The CDW patient table was used as the primary source for date of death, with the vital status file as a second source. Suicide mortality was evaluated using ICD-10 codes X60-X84 and Y87.043 in National Death Index (NDI) cause-of-death data (Ilgen et al., 2016).

EMULATION METHODS

We took the following steps to implement the trial emulation approach (Hernán and Robins, 2016):

- First, we determined whether each patient received one of the two active mutually exclusive opioid treatment strategies (small reduction or large reduction) within the 6-month treatment implementation period. Those who received neither active strategy were in the control (no reduction) group.
- Second, we created two datasets corresponding to the two sets of analyses comparing 1) small dose reduction vs. control and 2) large dose reduction vs. control.

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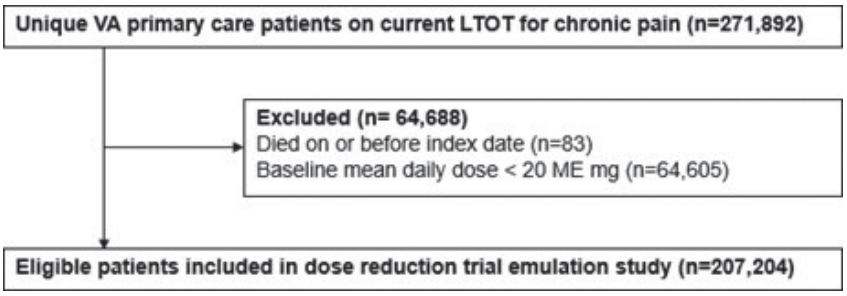

FIGURE F-1 Selection of patients.

KEY VARIABLES

- Within each dataset, patient records were replicated at the index date, creating "clones" that were assigned to the alternate treatment group (active dose reduction strategy or control). Clones assigned to an active dose reduction strategy were censored at 6 months (the end of the treatment implementation period) when the patient did not meet criteria for the active treatment strategy by 6 months. Clones assigned to the control group were censored when the patient met criteria for the active dose reduction strategy during the treatment implementation period. Annex 4 provides an illustration of cloning and censoring.
- Inverse-probability-of-censoring weights (IPCW) were created using a Cox regression model for each set of analyses. We used standardized differences to examine balance in potential confounding variables between active treatment and control in each dataset (Annex 5). We found only small differences in weighted variables, which indicates good balance of measured confounders.
- Two sets of IPCW-weighted Cox proportional hazards models were used for analysis of cloned data, to separately compare 1) small dose reduction vs. control and 2) large dose reduction vs. control. In each set, pre-planned analyses were conducted for baseline opioid daily dose strata (20 to <50 mg, 50-<100 mg, and 100+ mg) and presence or absence of benzodiazepine treatment at baseline
- Because cloning artificially increases the number of events, model-based standard errors (SE) may be underestimated. (Maringe et al., 2020) To check for this problem, we used non-parametric bootstrapping to obtain SE estimates for selected results. We found that bootstrapping did not produce substantially different SE estimates.

RESULTS

Baseline characteristics of eligible patients by treatment assignment and by 12-month vital status are shown in Annex 6 and Annex 7, respectively. Of the 207,204 eligible patients, 9,646 (4.7%) died of all causes during the year after the index date (Table F-2). The cause of death was suicide for 208 (2.2%) of deaths overall, including 18 (2.1%) of 851 patients who died with less than 1 month of observation. Suicide was the cause of death for 2.3% of all deaths in the control (no dose reduction) group, 2.7% of deaths in the small dose reduction group, and 1.5% of deaths in the large dose reduction group.

Table F-3 shows the main results of the trial emulation. During 1-year follow-up, there was no difference in risk of all-cause mortality between small reduction and control groups overall (HR 1.01, 95% CI 0.98, 1.04) or in the low and moderate baseline daily dose subgroups. There was a small, statistically significant increase in risk for the small reduction group within the high baseline daily dose subgroup.

All-cause mortality was statistically significantly higher for the large dose reduction group than the control group overall (HR 1.23; 95% CI 1.20, 1.27) and within each of the baseline daily dose subgroups.

Results for both small reduction vs. control and large reduction vs. control were similar among patients with and without concomitant benzodiazepine treatment at baseline.

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TABLE F-2 Unadjusted Deaths Within 1 Year According to Trial Emulation Treatment Group Assignment (n=207,204)

	Patients with at least one follow-up month			
	Small dose reduction group n=29,835	**Large dose reduction group n=46,734**	**Control (no dose reduction) group n=129,784**	**Patients who survived less than one month n=851**
All cause death, n (column %)	1056 (3.5%)	2008 (4.3%)	5731 (4.4%)	851 (100%)
Suicide death, n (column %)	28 (0.09%)	30 (0.06%)	132 (0.10%)	18 (2.1%)
Median 1-year survival in months [range]	7 [1-12]	8 [2-12]	6 [2-12]	NA

NOTE: NA = not applicable.

TABLE F-3 Weighted Estimates of the Effect of Dose Reduction Strategies vs. No Dose Reduction Control on Time to All-Cause Mortality With 1-Year Follow-Up Time, Overall and By Baseline Dosage Category, Hazard Ratio (95% CI)

	Small dose reduction group n=29,835	**Large dose reduction group n=46,734**
Overall	1.01 (0.98, 1.04)	1.23 (1.20, 1.27)
Baseline daily dose category		
Low (20 to < 50 mg)	0.98 (0.94, 1.02)	1.22 (1.17,1.27)
Moderate (50 to <100 mg)	1.01 (0.95,1.08)	1.25 (1.18,1.33)
High (100+ mg)	1.10 (1.02,1.19)*	1.25 (1.16, 1.35)
Baseline benzodiazepine treatment		
Benzodiazepine	1.06 (0.98, 1.15)	1.22 (1.13, 1.31)
No benzodiazepine	1.01 (0.97, 1.04)	1.23 (1.19, 1.27)

* Bootstrapped 95% CI =1.02, 1.17.

During 1-year follow-up, there was no difference in risk of suicide mortality for small reduction vs. control (HR 1.09, 95% CI 0.89, 1.35) or large reduction vs. control (HR 1.01, 95% CI 0.77, 1.33). Among patients who died during 1-year follow-up, there was no difference in risk of suicide death (as opposed to other cause of death) for small reduction vs. control (HR 1.11, 95% CI 0.89, 1.38) or large reduction vs. control (HR 0.88, 95% CI 0.71, 1.09).

EXPLORATORY ANALYSIS OF DOSING CHANGES

To better understand the main results, we explored opioid dosing changes within the assigned treatment groups. Figure F-2 shows the trajectories of mean daily dosage by treatment group within baseline daily dose categories.

By definition, only the large dose reduction group includes patients whose opioids were discontinued during the 6-month treatment implementation period. Of 46,734 patients in the large dose reduction treatment group, 30,802 (65.9%) had their daily opioid dosage reduced to zero (i.e., no dispensed opioids in a 60-day window) at some point during the 6-month treatment implementation period. Of these patients, more than half (n=16,646, 53.7%) subsequently filled opioid prescriptions during the remainder of the 12-month study period. Among those patients who had a zero dosage and subsequently filled additional opioid prescriptions, most restarted opioids within 1 month (Table F-4). This suggests the large dose reduction treatment group is heterogeneous in terms of opioid prescribing, comprising patients with reduction to a substantially lower dose, those with opioid discontinuation, and those with prolonged gaps or variability in opioid dispensing.

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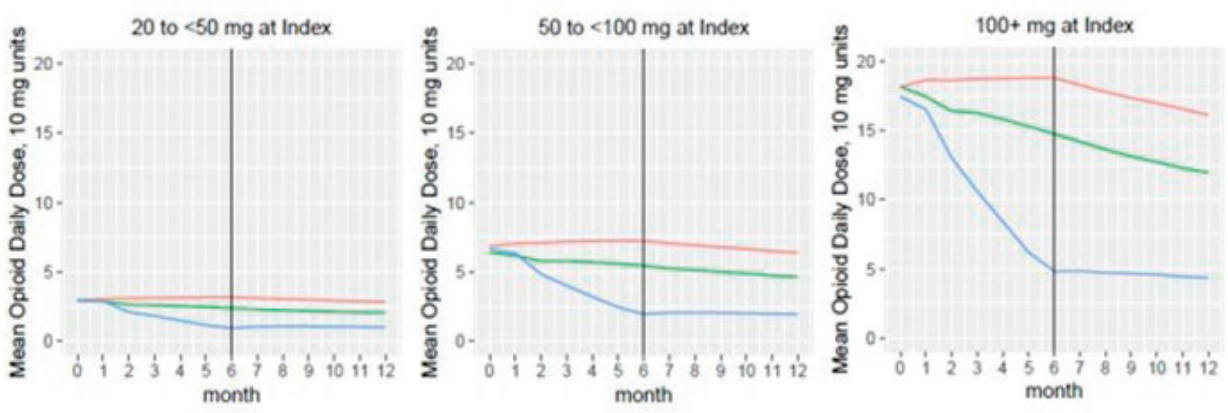

FIGURE F-2 Mean daily dosage over 12 months by treatment group, within baseline dose categories.
NOTES: Figure legend: red = control (no reduction) group, green = small reduction group, blue = large reduction group.

TABLE F-4 Timing of Opioid "Restart" Among 16,646 Patients Who Filled an Opioid Prescription After the First Month With a Daily Dosage of 0 mg

Months following zero dosage	1	2	3	4	5	6	7	8	9	10
Number (%) of patients who restarted	8978 (53.9%)	2924 (17.6%)	1466 (8.8%)	976 (5.9%)	742 (4.5%)	537 (3.2%)	403 (2.4%)	272 (1.6%)	169 (1.0%)	79 (0.5%)

To explore potential mortality risk within the large dose reduction treatment group, we repeated weighted Cox models with two subsets of patients: (a) those whose daily dosage remained more than 0 mg (n=15,932) and (b) those whose dosage decreased to 0 mg (n=30,802). Results are in Table F-5. In the subgroup with dosage > 0 mg, there was no difference in mortality risk between large dose reduction treatment and control. In the subgroup with a dosage of zero, risk of all-cause mortality was higher for the treatment group vs. control.

TABLE F-5 Weighted Estimates of the Effect of Dose Reduction Strategies vs. No Dose Reduction Control on Time to All-Cause Mortality With 1-Year Follow-Up Time, Overall and By Baseline Dosage Category, With Exploratory Subgroup Analysis Within Large Dose Reduction Treatment Group, Hazard Ratio (95% CI)

	Small dose reduction group N=29,835	**Large dose reduction group N=46,734**	
		Daily dosage > 0 mg N=15,932	Daily dosage = 0 mg N=30,802
Overall	1.01 (0.98, 1.04)	1.03 (0.97, 1.10)	1.33 (1.30, 1.38)
Baseline daily dose category			
Low (20 to < 50 mg)	0.98 (0.94, 1.02)	1.03 (0.98, 1.07)	1.28 (1.23, 1.33)
Moderate (50 to <100 mg)	1.01 (0.95,1.08)	1.02 (0.95, 1.09)	1.41 (1.32, 1.50)
High (100+ mg)	1.10 (1.02,1.19)	1.07 (0.98, 1.16)	1.46 (1.35, 1.58)

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LIMITATIONS AND NEXT STEPS

- The presented results are design-dependent and should be interpreted with care. By design-dependent, we mean that results are affected by decisions including intervention definitions, assignment of interventions based on a single dosage decrease during the implementation period, the chosen baseline calendar year (2016), the 6-month implementation period and relatively short (12 months) follow-up time, and the treatment of patients with apparent opioid discontinuation (defined as zero daily dosage).
- The trial emulation approach evaluates effects of treatment strategies defined at a point in time within a pre-defined treatment implementation period, but prescribing changes are dynamic in reality. Further, variability in opioid dosing/dispensing is associated with overdose and not addressed by this study design (Glanz et al., 2019).
- Approaches to defining opioid dose change exposures have tradeoffs in terms of sensitivity for detecting changes in the presence of common factors as multiple opioids, overlapping prescriptions, and variable dispensing dates. Seemingly small changes in exposure definitions can affect results.
- The study population is large and diverse. Opioid dose reduction strategies may have differing effects in various patient subgroups defined by clinical conditions (e.g., substance use disorder) or characteristics (e.g., old age).
- The trial emulation approach does not eliminate bias caused by unmeasured confounding. For example, common reasons for opioid dose reduction and discontinuation are behaviors (e.g., opioid misuse) and clinical signs (e.g., sedation) that increase the risk of death and are not well captured in CDW data.
- Suicide deaths are rare events, so we have limited power to detect differences between treatments.

We are using alternative analytic approaches to model dose decreases both as a static (non-time-varying) intervention and as a dynamic time-varying intervention. Completion of additional analyses will provide context for interpretation of trial emulation results.

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ANNEX 1. EPOCH POPULATION COHORT INCLUSION AND EXCLUSION CRITERIA

The study population was defined as community-dwelling VA primary care patients receiving long-term opioid analgesic therapy (LTOT) for chronic pain.

Criteria	Definition
Inclusion criteria	
VA primary care	At least one encounter in a primary care clinic (stop codes 322, 323) within the 12 months before the most recent opioid prescription.
Current long-term opioid therapy	A qualifying opioid analgesic* dispensed within the prior 30 days and 150 days' supply of qualifying opioid with no gaps >40 days between fills in the 180 days before the most recent dispensing date.
Exclusion criteria	
Opioid use disorder treatment	Any outpatient encounter in prior 12 months with a code for Opioid Substitution (523).
Dementia	Any outpatient encounter in prior 12 months with a code for Dementia Clinic (320); any problem list or outpatient encounter in the prior 12 months with any of the following diagnosis codes: ICD-9 290, 290.1, 290.11, 290.12, 290.13, 290.2, 290.21, 290.3, 290.4, 290.41, 290.42, 290.43, 290.8, 290.9, 331, 331.1, 331.11, 331.19, 331.2, 331.6, 331.7, 331.82 or ICD-10 F01.5, F01.50, F01.51, F02.80, F02.81, F03.90, F03.91, G30.0, G30.1, G30.8, G30.9, G31.01, G31.09, G31.1,G31.83, R41.81
Cancer treatment	Any outpatient encounter in prior 12 months with a code for Radiation Oncology/ Therapy (149), Brachytherapy (158), or Oncology Tumor (316)
End-of-life care	Any outpatient encounter in prior 12 months with a code for Hospice Care (351) or Palliative Care (353)
Adult day care	Any outpatient encounter in prior 12 months with a code for Adult Day Health Care (190), Community Adult Day Health Care Follow-up (191)
Nursing home residence	An inpatient census record without a corresponding discharge; index opioid dispensed between admission and discharge dates for any of the following bed section codes: Respite Care NHCU (47), NH Short Stay Restorative (66), NH Short Stay Continuing Care (67), NH Short Stay Mental Health (68), NH Short Stay Dementia Care (69), Nursing Home Care (80), NH Short Stay Skilled Nursing (95), Hospice (96), Short Stay GRECC NHCU (100), Long Stay GRECC NHCU (101), Short Stay GRECC GEM NHCU (102), or Hospice for Acute Care (105)

*See Annex 2. Opioid formulations and dosage conversion factors.

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ANNEX 2. OPIOID FORMULATIONS AND DOSAGE CONVERSION FACTORS

TABLE F-6 Qualifying Opioid Analgesics Indicated for Chronic Pain Treatment with Conversion Factors for Dosage Calculations

Opioid	Included formulation(s)	Conversion factor
Codeine	Capsule, elixir, tablet; sole ingredient and combination products including acetaminophen, butalbital, caffeine	0.15
Fentanyl	Patch	7.2
Hydrocodone	Capsule, elixir, tablet; sole ingredient and combination products including acetaminophen, ibuprofen; immediate release and sustained action	1
Hydromorphone	Suppository, tablet; immediate release and sustained action	4
Levorphanol	Tablet	11
Meperidine	Tablet	0.1
Methadone	Tablet, solution	3
Morphine	Capsule, solution, suppository, tablet; immediate release and sustained action	1
Oxycodone	Capsule, solution, tablet; sole ingredient and combination products including acetaminophen; immediate release and sustained action	1.5
Oxymorphone	Tablet; immediate release and sustained action	3
Pentazocine	Tablet	0.37
Tapentadol	Tablet; sustained action	1
Non-qualifying opioids with conversion factors if applicable for dosage calculations		
Opioid	Non-qualifying formulation(s) and rationale	Conversion factor
All	Injectable solutions (indicated for acute or palliative care)	n/a
All	Combination products including antitussives or antihistamines (indicated for cough)	n/a
Buprenorphine	Patch (added to VA formulary in July 2016; limited use in VA)	2.2
Buprenorphine	Sublingual tablets and films (indicated for opioid use disorder)	n/a
Fentanyl	Lozenge (indicated for cancer or palliative care)	0.13
Tramadol	All formulations (weak opioid agonist)	0.1

SOURCE: National Center for Injury Prevention and Control. CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2018 version. Available from: https://www.cdc.gov/drugoverdose/resources/data.html.

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ANNEX 3. ILLUSTRATION OF OPIOID DOSAGE CALCULATIONS

Baseline daily opioid dosage was calculated as the total dosage for all opioids dispensed in 60 days before and including index date divided by the number of days from the first opioid dispensed in the window to the index prescription's end date (i.e., dispensing date + days' supply). Follow-up daily opioid dosage was calculated as the average daily dosage at successive calendar months: the total opioid dosage dispensed over the prior 60 days divided by the number of days from the first dispensing date in the window to the end date of the last prescription dispensed in the window.

The figure illustrates opioid dispensing data and calculation of baseline and follow-up opioid daily dosages for a hypothetical patient with an index date of June 1. For this patient, the average daily dosage for the December 1 time point was calculated using the three prescriptions that fell within the prior 60 days. The average daily dosage for the December 1 time point was calculated by summing the total dosage dispensed for the three prescriptions divided by the number of days from when the first prescription was released to when the third prescription was released plus the 28 days' supply of the last prescription.

Dispensed opioid prescriptions are shown above the timeline, with d=days' supply. 60-day dosage windows overlap as shown by the horizontal green bars. Different colors represent different opioid medications.

Prescriptions contribute to the overlapping 60-day average dose windows as shown by the shaded vertical bars.

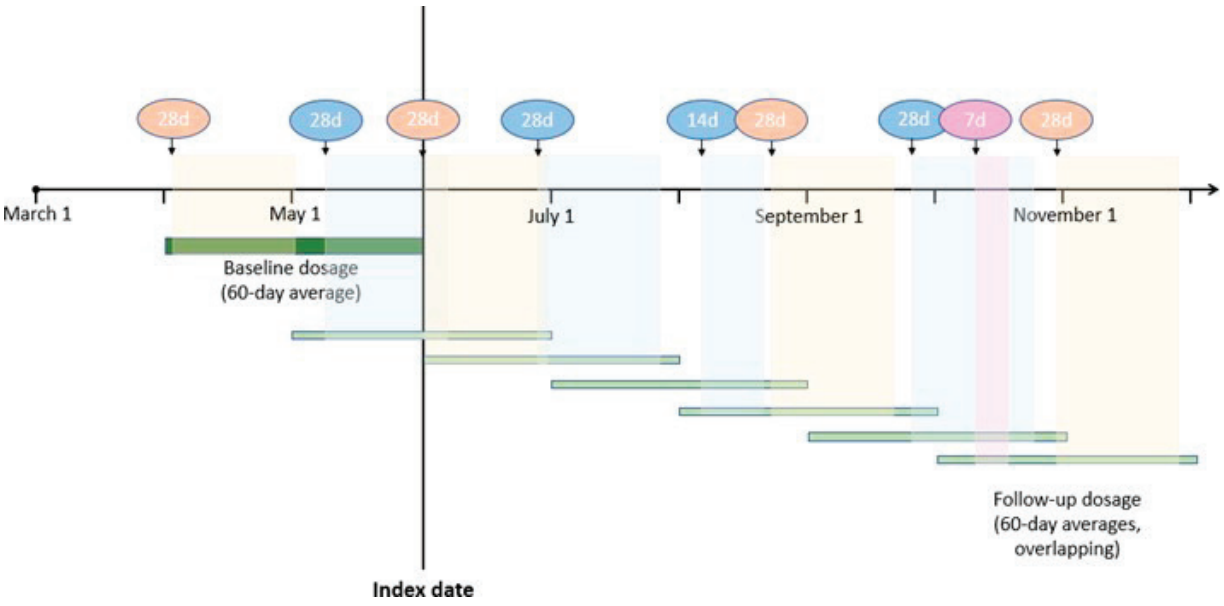

FIGURE F-3 Opioid dosage for a hypothetical patient.

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ANNEX 4. ILLUSTRATION OF TRIAL EMULATION DESIGN

Eligibility is assessed over the 6 months prior to each patient's index date. The treatment implementation period comprises the 6 months following the index date. Outcomes are assessed over the 12 months following the index date.

The figure shows the cloning and censoring approach for two example patients. Patient 1 had a 20% drop in opioid dose at month 2, causing the clone in the control arm to be censored, while the clone in the small reduction arm was followed until the end of outcome assessment at 12 months. Patient 2 had a 60% drop in opioid dose at month 4, causing the clone in the control arm to be censored, while the clone in the large reduction arm was followed until the end of outcome assessment at 12 months.

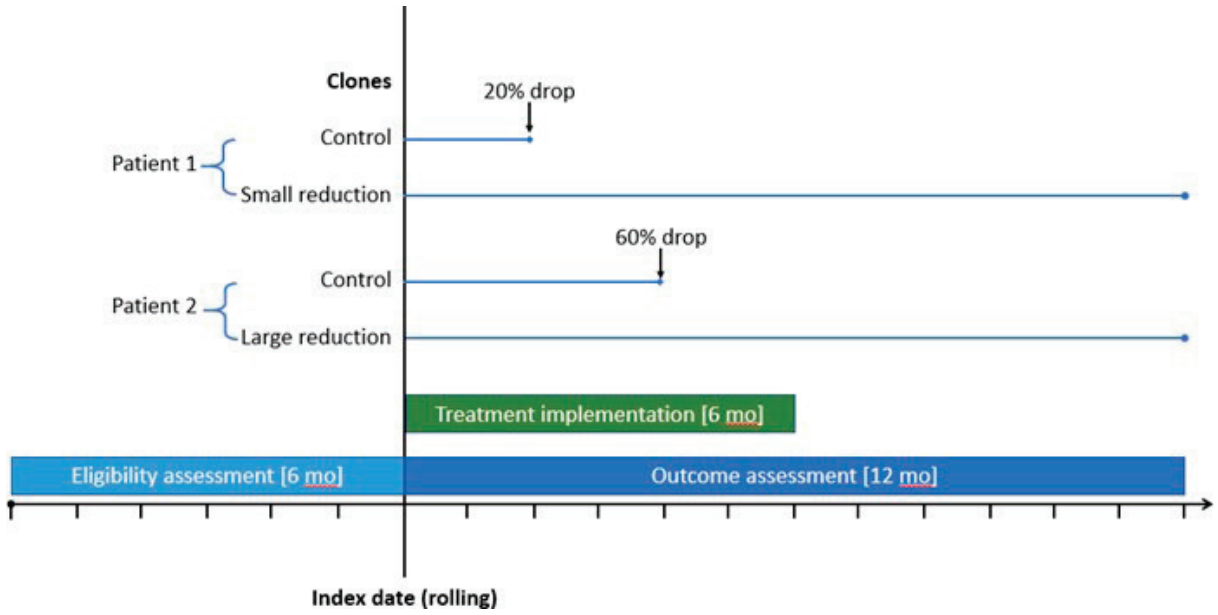

FIGURE F-4 Cloning and censoring for two hypothetical patients.

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ANNEX 5. BALANCE OF WEIGHTED AND UNWEIGHTED COVARIATES

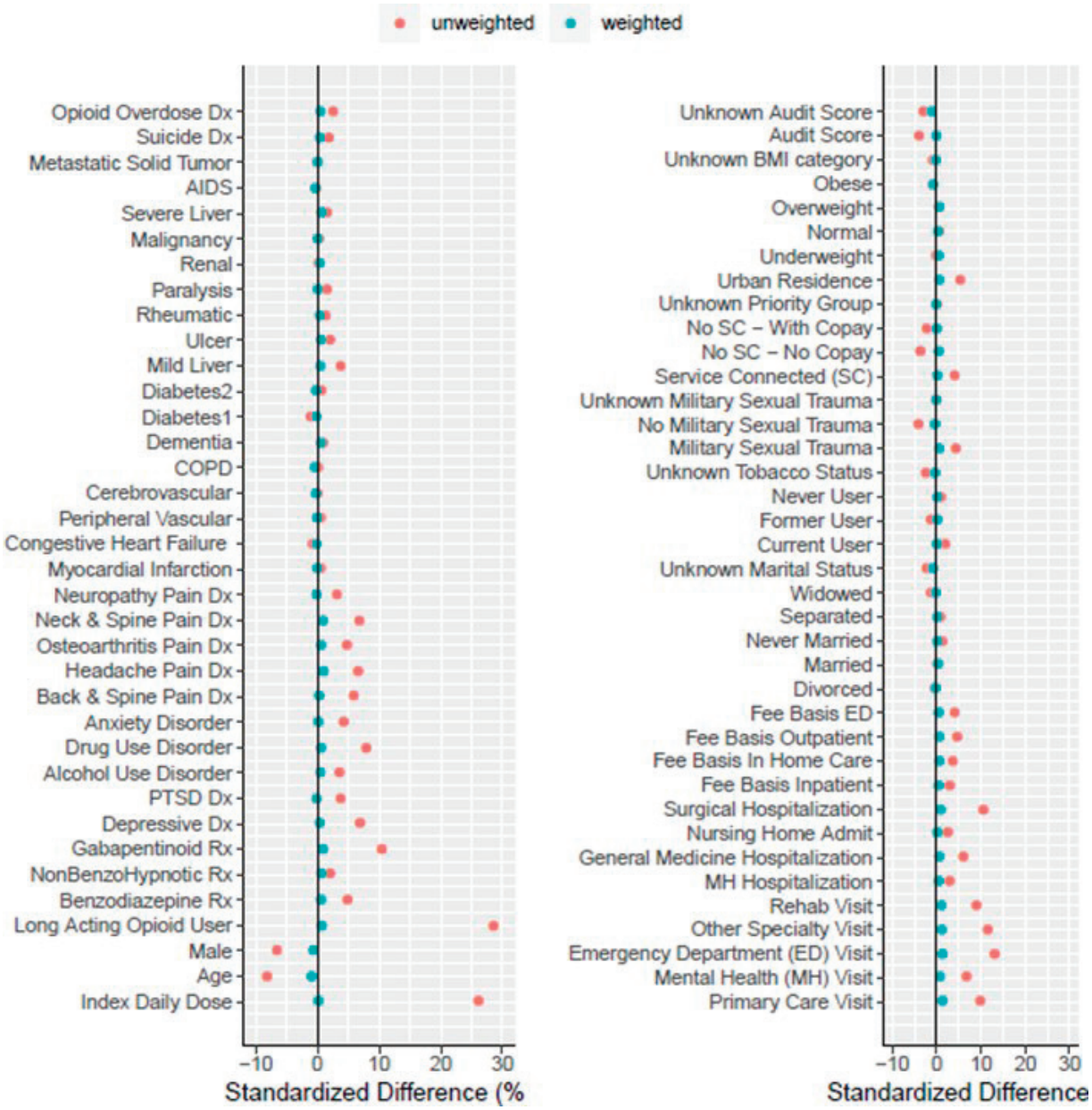

FIGURE F-5 Standardized mean difference (%) in potential confounders at 6 months after inverse- probability-of-censoring weighting (IPCW) for small decrease group versus no decrease group.
NOTE: AUDIT score and BMI were not included in final models due to missing data.

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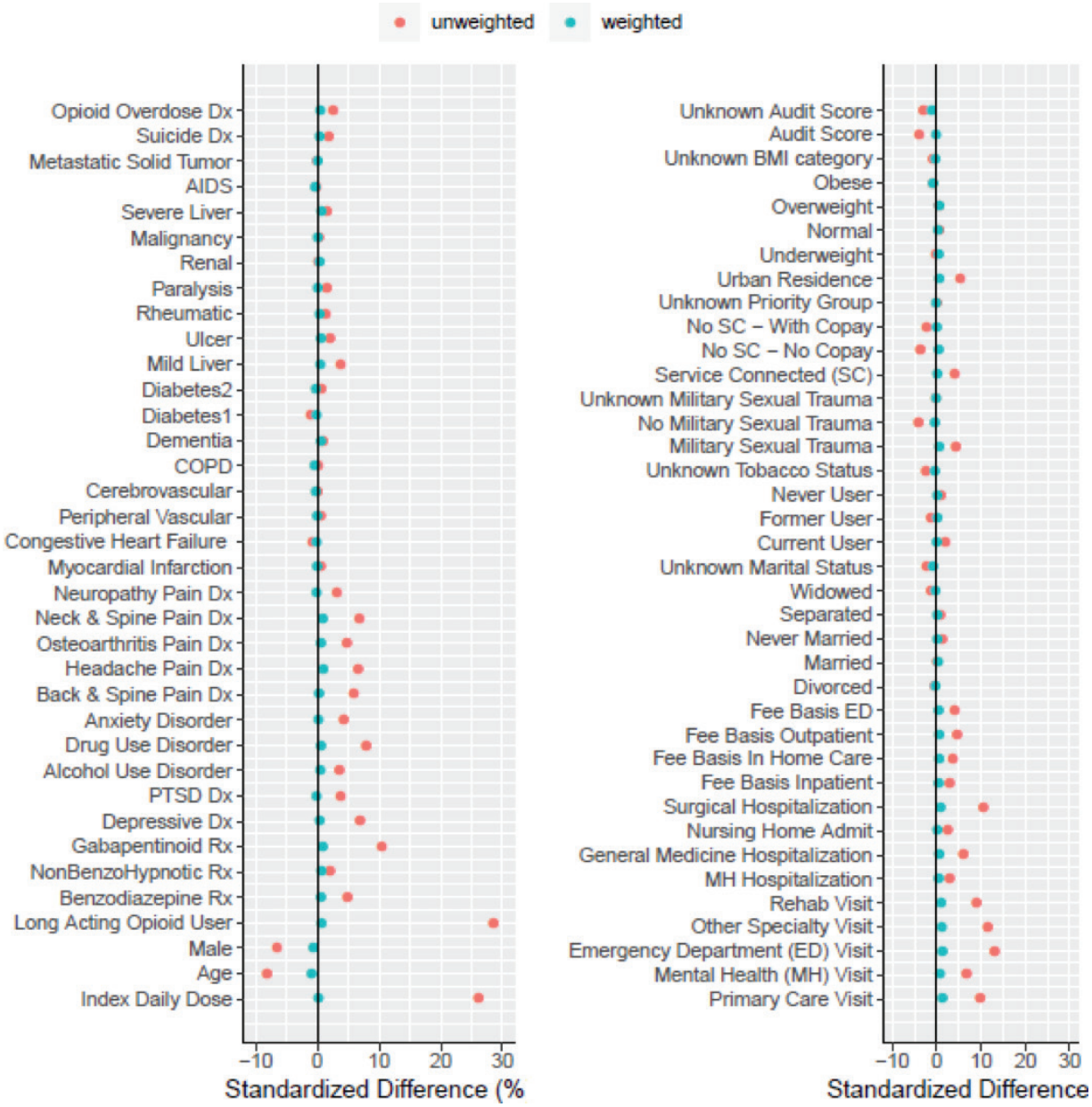

FIGURE F-6 Standardized mean difference (%) in potential confounders at 6 months after inverse- probability-of-censoring weighting (IPCW) for the large decrease group versus no decrease group.
NOTE: AUDIT score and BMI were not included in final models due to missing data.

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ANNEX 6: BASELINE CHARACTERISTICS BY TREATMENT GROUP

TABLE F-7 Baseline Characteristics by Trial Emulation Treatment Group Assignment for Patients Who Had at Least One Follow-Up Data Point* (N=206,353)

Trial emulation treatment group defined by opioid daily dose change from baseline within 6 months			
Characteristic	**Large dose reduction N=46,734 (22.6%)**	**Small dose reduction N=29,835 (14.4%)**	**No dose reduction N=129,784 (62.6%)**
Age in Years	61.2 (12.4)	61.6 (11.4)	62.5 (11.2)
Sex, Male	43101 (92.2%)	27478 (92.1%)	121600 (93.7%)
Race[1]			
White	36193 (77.4%)	23418 (78.5%)	101857 (78.5%)
Black	7092 (15.2%)	4285 (14.4%)	18295 (14.1%)
American Indian	686 (1.5%)	445 (1.5%)	1935 (1.5%)
Asian	148 (0.3%)	94 (0.3%)	386 (0.3%)
Pacific Islander	486 (1.0%)	298 (1.0%)	1371 (1.1%)
Unknown	2560 (5.5%)	1614 (5.4%)	7259 (5.6%)
Hispanic Ethnicity			
Yes	1905 (4.1%)	1196 (4.0%)	4673 (3.6%)
No	43186 (92.4%)	27593 (92.5%)	120495 (92.8%)
Unknown	1643 (3.5%)	1046 (3.5%)	4616 (3.6%)
Marital Status			
Married	23537 (50.4%)	15640 (52.4%)	68006 (52.4%)
Never Married	4384 (9.4%)	2646 (8.9%)	11071 (8.5%)
Divorced	14115 (30.2%)	8775 (29.4%)	38378 (29.6%)
Separated	2170 (4.6%)	1340 (4.5%)	5605 (4.3%)
Widowed	2230 (4.8%)	1320 (4.4%)	6021 (4.6%)
Unknown	298 (0.6%)	114 (0.4%)	703 (0.5%)
Urban Residence	26699 (57.1%)	16923 (56.7%)	70208 (54.1%)
VA Enrollment Priority Group			
Service Connected (SC; group 1-4)	28802 (61.6%)	18507 (62.0%)	77992 (60.1%)
Not SC, No Copay (group 5-6)	14017 (30.0%)	8919 (29.9%)	40002 (30.8%)
Not SC, with Copay (group 7-8)	3770 (8.1%)	2336 (7.8%)	11469 (8.8%)
Unknown	145 (0.3%)	73 (0.2%)	321 (0.2%)
Post-9/11 Military Service	3322 (7.1%)	1687 (5.7%)	6522 (5.0%)
Military Sexual Trauma			
Yes	2306 (4.9%)	1453 (4.9%)	5214 (4.0%)
No	44277 (94.7%)	28299 (94.9%)	124196 (95.7%)
Unknown	151 (0.3%)	83 (0.3%)	374 (0.3%)
Tobacco Use Status			
Current	20975 (44.9%)	13460 (45.1%)	57312 (44.2%)
Former	12318 (26.4%)	8336 (27.9%)	37023 (28.5%)
Never	7978 (17.1%)	5007 (16.8%)	21344 (16.4%)
Unknown	5463 (11.7%+)	3032 (10.2%)	14105 (10.9%)

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE F-7 Continued

Characteristic	Large dose reduction N=46,734 (22.6%)	Small dose reduction N=29,835 (14.4%)	No dose reduction N=129,784 (62.6%)
BMI Category[2]			
Below 18.5: Underweight	820 (1.8%)	439 (1.5%)	1899 (1.5%)
18.5 to < 25: Normal	8969 (19.2%)	5373 (18.0%)	23001 (17.8%)
25 to <30: Overweight	14473 (31.1%)	9267 (31.1%)	40073 (30.9%)
30+: Obese	22342 (47.9%)	14712 (49.4%)	64588 (49.9%)
Pain Diagnoses[3]			
Back/Spine Disorders	32075 (68.6%)	20835 (69.8%)	87119 (67.1%)
Neck/Spine Disorders	10283 (22.0%)	6692 (22.4%)	25617 (19.7%)
Osteoarthritis	14583 (31.2%)	9094 (30.5%)	36752 (28.3%)
Neuropathy	9365 (20.0%)	6019 (20.2%)	24477 (18.9%)
Headache	4120 (8.8%)	2606 (8.7%)	9129 (7.0%)
Mental Health Diagnoses[3]			
Depressive Disorder	14190 (30.4%)	9144 (30.6%)	35791 (27.6%)
Anxiety Disorder	7658 (16.4%)	4706 (15.8%)	18522 (14.3%)
PTSD	12090 (25.9%)	7196 (24.1%)	29280 (22.6%)
Alcohol Use Disorder (AUD)	3749 (8.0%)	1950 (6.5%)	7367 (5.7%)
Drug Use Disorder	4193 (9.0%)	2280 (7.6%)	7477 (5.8%)
Opioid Use Disorder	2225 (4.8%)	1400 (4.7%)	4247 (3.3%)
AUD Identification Test (AUDIT) Score[2]	0.94 (1.79)	0.80 (1.60)	0.87 (1.65)
Suicide-Related Diagnosis	139 (0.3%)	70 (0.2%)	203 (0.2%)
Opioid Overdose Diagnosis	98 (0.2%)	60 (0.2%)	139 (0.1%)
Charlson Comorbidity Index Score[3]	1.47 (1.78)	1.47 (1.76)	1.44 (1.72)
Charlson Index Conditions[3]			
Myocardial Infarction	1305 (2.8%)	779 (2.6%)	3249 (2.5%)
Congestive Heart Failure	3704 (7.9%)	2289 (7.7%)	10061 (7.8%)
Peripheral Vascular Disease	2078 (4.4%)	1185 (4.0%)	4976 (3.8%)
Cerebrovascular Disease	1566 (3.4%)	826 (2.8%)	3560 (2.7%)
COPD	11436 (24.5%)	7381 (24.7%)	31855 (24.5%)
Dementia	168 (0.4%)	86 (0.3%)	305 (0.2%)
Diabetes without Complications	15125 (32.4%)	9875 (33.1%)	43507 (33.5%)
Diabetes with Complications	7059 (15.1%)	4575 (15.3%)	19511 (15.0%)
Mild Liver Disease	3875 (8.3%)	2533 (8.5%)	9680 (7.5%)
Moderate or Severe Liver Disease	356 (0.8%)	217 (0.7%)	759 (0.6%)
Peptic Ulcer Disease	526 (1.1%)	362 (1.2%)	1283 (1.0%)
Rheumatic Disease	1236 (2.6%)	863 (2.9%)	3470 (2.7%)
Hemiplegia or Paraplegia	593 (1.3%)	391 (1.3%)	1475 (1.1%)
Renal Disease	3803 (8.1%)	2350 (7.9%)	10070 (7.8%)
Any Malignancy	3654 (7.8%)	2406 (8.1%)	10275 (7.9%)
Metastatic Solid Tumor	317 (0.7%)	212 (0.7%)	886 (0.7%)
AIDS/HIV	194 (0.4%)	103 (0.3%)	465 (0.4%)

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE F-7 Continued

Characteristic	Large dose reduction N=46,734 (22.6%)	Small dose reduction N=29,835 (14.4%)	No dose reduction N=129,784 (62.6%)
Admissions in Prior Year			
Any Mental Health Hospitalization	772 (1.7%)	284 (1.0%)	900 (0.7%)
Any Medical Hospitalization	4366 (9.3%)	2731 (9.2%)	9651 (7.4%)
Any Surgical Hospitalization	2925 (6.3%)	1696 (5.7%)	4679 (3.6%)
Any Nursing Home Admission	363 (0.8%)	168 (0.6%)	501 (0.4%)
VA Visits, Number in Prior Year			
Primary Care Visits	4.7 (4.1)	4.7 (4.2)	4.3 (3.8)
Mental Health Visits	4.4 (12.3)	3.9 (11.0)	3.3 (9.6)
Emergency Department Visits	1.0 (2.2)	0.9 (2.0)	0.7 (1.6)
Rehabilitation Visits	2.7 (7.2)	2.6 (6.9)	2.0 (6.3)
Specialty Clinic Visits	5.3 (7.4)	5.5 (7.3)	4.7 (6.6)
Any Fee Basis in Prior Month			
Inpatient Care	639 (1.4%)	275 (0.9%)	786 (0.6%)
Home Health Care	1741 (3.7%)	957 (3.2%)	3332 (2.6%)
Outpatient Care	3151 (6.7%)	1735 (5.8%)	6180 (4.8%)
Emergency Department	1223 (2.6%)	650 (2.2%)	2042 (1.6%)
Opioid Daily Dose in Prior 60 Days			
ME mg/Day, Mean (SD)	56.9 (58.7)	75.0 (78.0)	57.6 (60.9)
ME mg/Day, Median (IQR)	40.0 (30.7)	48.7 (59.5)	40.0 (30.7)
20 to < 50 mg	31269 (66.9%)	15055 (50.5%)	87964 (67.8%)
50 to < 100 mg	9946 (21.3%)	8320 (27.9%)	26637 (20.5%)
100+ mg	5519 (11.8%)	6460 (21.7%)	15183 (11.7%)
Opioid Formulation in Prior 60 Days			
Any Long-Acting	12844 (27.5%)	11271 (37.8%)	32541 (25.1%)
Short-Acting Only	33890 (72.5%)	18564 (62.2%)	97243 (74.9%)
Benzodiazepine in Prior 60 Days	7660 (16.4%)	4998 (16.8%)	19433 (15.0%)
Non-Benzo Hypnotic in Prior 60 Days	3661 (7.8%)	2455 (8.2%)	9940 (7.7%)
Gabapentinoid in Prior 60 Days	12626 (27.0%)	8836 (29.6%)	32445 (25.0%)

[1] 18,511 missing AUDIT Score and 410 missing BMI.

[2] From ICD-9 and ICD-10 diagnoses in the prior 12 months.

[3] Includes opioid use disorder.

NOTES: 851 died before the 1-month follow-up time point and were therefore not assigned to a treatment group. Categories are not mutually exclusive.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

ANNEX 7: BASELINE CHARACTERISTICS BY VITAL STATUS

TABLE F-8 Baseline Characteristics by Vital Status at 1 Year (n=207,204)

Characteristic	Total N=207,204	Alive N=197,558 (95.3%)	Dead (all cause) N=9,646 (4.7%)	Dead (suicide cause) N=208 (0.1%)
Age in Years	62.1 (11.5)	61.8 (11.5)	69.5 (10.1)	63.5 (12.9)
Sex, Male	193002 (93.1%)	183654 (93.0%)	9348 (97%)	205 (98.6%)
Race[1]				
White	162177 (78.3%)	154203 (78.1%)	7974 (82.7%)	186 (89.4%)
Black	29743 (14.4%)	28835 (14.6%)	908 (9.4%)	1 (0.5%)
American Indian	3077 (1.5%)	2952 (1.5%)	125 (1.3%)	2 (0.1%)
Asian	628 (0.3%)	615 (0.3%)	13 (0.1%)	0
Pacific Islander	2160 (1.0%)	2079 (1.1%)	81 (0.8%)	0
Unknown	11493 (5.5%)	10859 (5.5%)	634 (6.6%)	20 (9.6%)
Hispanic Ethnicity				
Yes	7801 (3.8%)	7543 (3.8%)	258 (2.7%)	4 (1.9%)
No	192051 (92.7%)	183065 (92.7%)	8986 (93.2%)	188 (90.4%)
Unknown	7352 (3.5%)	6950 (3.5%)	402 (4.2%)	16 (7.7%)
Marital Status				
Married	107587 (51.9%)	102990 (52.1%)	4597 (47.7%)	83 (39.9%)
Never Married	18175 (8.8%)	17513 (8.9%)	662 (6.9%)	17 (8.2%)
Divorced	61523 (29.7%)	58510 (29.6%)	3013 (31.2%)	84 (40.4%)
Separated	9147 (4.4%)	8749 (4.4%)	398 (4.1%)	8 (3.8%)
Widowed	9649 (4.7%)	8753 (4.4%)	896 (9.3%)	14 (6.7%)
Unknown	1123 (0.5%)	1043 (0.5%)	80 (0.8%)	2 (0.1%)
Urban residence	114244 (55.1%)	109261 (55.3%)	4983 (51.7%)	102 (49.0%)
VA Enrollment Priority Group				
Service Connected (SC; group 1-4)	125720 (60.7%)	120943 (61.2%)	4777 (49.5%)	101 (48.6%)
Not SC, No Copay (group 5-6)	62394 (30.5%)	59349 (30.0%)	3945 (40.9%)	83 (39.9%)
Not SC, with Copay (group 7-8)	17650 (8.5%)	16737 (8.5%)	913 (9.5%)	24 (11.5%)
Unknown	540 (0.3%)	529 (0.3%)	11 (0.1%)	0 (0.0%)
Post-9/11 Military Service	11538 (5.6%)	11449 (5.8%)	89 (0.9%)	10 (4.8%)
Military Sexual Trauma				
Yes	8995 (4.3%)	8736 (4.4%)	259 (2.7%)	9 (4.3%)
No	197499 (95.4%)	188231 (95.3%)	9368 (97.1%)	198 (95.2%)
Unknown	610 (0.3%)	591 (0.3%)	19 (0.2%)	1 (0.5%)
Tobacco Use Status				
Current User	92085 (44.4%)	87809 (44.4%)	4276 (44.3%)	106 (51.0%)
Former User	57918 (28.0%)	55150 (27.9%)	2768 (28.7%)	46 (22.1%)
Never User	34442 (16.6%)	33128 (16.8%)	1314 (13.6%)	27 (13.0%)
Unknown	22759 (11.0%)	21471 (10.9%)	1288 (13.4%)	29 (13.9%)

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE F-8 Continued

Characteristic	Total N=207,204	Alive N=197,558 (95.3%)	Dead (all cause) N=9,646 (4.7%)	Dead (suicide cause) N=208 (0.1%)
BMI Category[2]				
Below 18.5: Underweight	3216 (1.6%)	2627 (1.3%)	589 (6.2%)	2 (1.0%)
18.5 to < 25: Normal	37572 (18.2%)	34808 (17.6%)	2764 (28.9%)	59 (28.5%)
25 to <30: Overweight	64025 (31.0%)	61451 (31.2%)	2574 (26.9%)	65 (31.4%)
30+: Obese	101981 (49.3%)	98343 (49.9%)	3638 (38.0%)	81 (39.1%)
Pain Diagnoses[3]				
Back/Spine Disorders	140549 (67.8%)	134767 (68.2%)	5782 (59.9%)	135 (64.9%)
Neck/Spine Disorders	42731 (20.6%)	41302 (20.9%)	1429 (14.8%)	42 (20.2%)
Osteoarthritis	60671 (29.2%)	57883 (29.3%)	2788 (28.9%)	50 (24.0%)
Neuropathy	40082 (19.3%)	37561 (19.0%)	2521 (26.1%)	45 (21.6%)
Headache	15887 (7.7%)	15509 (7.9%)	378 (3.9%)	18 (8.7%)
Mental Health Diagnoses[3]				
Depressive Disorder	59327 (28.6%)	57001 (28.9%)	2326 (24.1%)	69 (33.2%)
Anxiety Disorder	30978 (15.0%)	29688 (15.0%)	1290 (13.4%)	43 (20.7%)
PTSD	48709 (23.5%)	47013 (23.8%)	1696 (17.6%)	45 (21.6%)
Alcohol Use Disorder (AUD)	13131 (6.3%)	12370 (6.3%)	761 (7.9%)	13 (6.2%)
Drug Use Disorder[4]	14000 (6.8%)	13320 (6.7%)	680 (7.0%)	30 (14.4%)
Opioid Use Disorder	7903 (3.8%)	7519 (3.8%)	384 (4.0%)	19 (9.1%)
AUD Identification Test (AUDIT) Score[2]	0.88 (1.68)	0.88 (1.67)	0.78 (1.77)	0.96 (1.93)
Suicide-Related Diagnosis	413 (0.2%)	389 (0.2%)	24 (0.2%)	4 (1.9%)
Opioid Overdose Diagnosis	300 (0.1%)	261 (0.1%)	39 (0.4%)	1 (0.5%)
Charlson Comorbidity Index Score[3]	1.46 (1.75)	1.38 (1.67)	2.99 (2.59)	1.50 (1.79)
Charlson Index Conditions[3]				
Myocardial Infarction	5388 (2.6%)	4785 (2.4%)	603 (6.3%)	6 (2.9%)
Congestive Heart Failure	16299 (7.9%)	14112 (7.1%)	2187 (22.7%)	11 (5.3%)
Peripheral Vascular Disease	8330 (4.0%)	7393 (3.7%)	937 (9.7%)	10 (4.8%)
Cerebrovascular Disease	6015 (2.9%)	5410 (2.7%)	605 (6.3%)	6 (2.9%)
COPD	51082 (24.7%)	46685 (23.6%)	4397 (45.6%)	68 (32.7%)
Dementia	574 (0.3%)	489 (0.2%)	85 (0.9%)	1 (0.5%)
Diabetes without Chronic Complications	68892 (33.2%)	64746 (32.8%)	4146 (43.0%)	59 (28.4%)
Diabetes with Chronic Complications	31363 (15.1%)	29101 (14.7%)	2262 (23.5%)	24 (11.5%)
Mild Liver Disease	16183 (7.8%)	15006 (7.6%)	1177 (12.2%)	25 (12.0%)
Peptic Ulcer Disease	2197 (1.1%)	1997 (1.0%)	200 (2.1%)	0 (0.0%)
Rheumatic Disease	5595 (2.7%)	5251 (2.7%)	344 (3.6%)	5 (2.4%)
Hemiplegia or Paraplegia	2477 (1.2%)	2313 (1.2%)	164 (1.7%)	7 (3.4%)
Renal Disease	16390 (7.9%)	14573 (7.4%)	1817 (18.8%)	19 (9.1%)
Any Malignancy	16527 (8.0%)	14508 (7.3%)	2019 (20.9%)	16 (7.7%)
Moderate or Severe Liver Disease	1355 (0.7%)	1118 (0.6%)	237 (2.5%)	0 (0.0%)
AIDS/HIV	765 (0.4%)	727 (0.4%)	38 (0.4%)	0 (0.0%)
Metastatic Solid Tumor	1463 (0.7%)	967 (0.5%)	496 (5.1%)	2 (1.0%)

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TABLE F-8 Continued

Characteristic	Total N=207,204	Alive N=197,558 (95.3%)	Dead (all cause) N=9,646 (4.7%)	Dead (suicide cause) N=208 (0.1%)
Admissions in Prior Year				
Any Mental Health Hospitalization	1964 (0.9%)	1876 (0.9%)	88 (0.9%)	7 (3.4%)
Any Medical Hospitalization	16917 (8.2%)	15080 (7.6%)	1837 (19.0%)	18 (8.7%)
Any Surgical Hospitalization	9348 (4.5%)	8792 (4.5%)	556 (5.8%)	10 (4.8%)
Any Nursing Home Admission	1046 (0.5%)	940 (0.5%)	106 (1.1%)	2 (1.0%)
VA Visits, Number in Prior Year				
Primary Care Visits	4.4 (3.9)	4.4 (3.9)	5.1 (4.9)	4.4 (5.5)
Mental Health Visits	3.6 (10.5)	3.7 (10.5)	2.6 (10.1)	4.4 (16.0)
Emergency Department Visits	0.8 (1.8)	0.8 (1.8)	1.1 (2.3)	0.7 (1.5)
Rehabilitation Visits	2.3 (6.6)	2.3 (6.6)	2.2 (6.8)	1.9 (6.0)
Specialty Clinic Visits	5.0 (6.9)	4.9 (6.7)	6.6 (9.6)	4.0 (7.5)
Any Fee Basis in Prior Month				
Inpatient Care	1791 (0.9%)	1403 (0.7%)	388 (0.4%)	3 (1.4%)
Home Health Care	6131 (3.0%)	5240 (2.7%)	891 (9.2%)	8 (3.8%)
Outpatient Care	11144 (5.4%)	10402 (5.3%)	742 (7.7%)	12 (5.8%)
Emergency Department	4014 (1.9%)	3531 (1.8%)	483 (5.0%)	6 (2.9%)
Opioid Daily Dose in Prior 60 Days				
ME mg/Day, Mean (SD)	60.0 (63.5)	59.6 (63.0)	68.3 (73.5)	70.9 (71.0)
ME mg/Day, Median (IQR)	40.0 (32.2)	40 (32.07)	41.5 (45.0)	46.3 (55.5)
20 to < 50 mg	134779 (65.0%)	129077 (65.3%)	5702 (59.1%)	110 (52.9%)
50 to < 100 mg	45118 (21.8%)	42796 (21.7%)	2322 (24.1%)	66 (31.7%)
100+ mg	27307 (13.2%)	25685 (13.0%)	1622 (16.8%)	32 (15.4%)
Opioid Formulation in Prior 60 Days				
Any Long-Acting	56920 (27.5%)	53876 (27.3%)	3044 (31.6%)	68 (32.7%)
Short-Acting Only	150284 (72.5%)	143682 (72.7%)	6602 (68.4%)	140 (67.3%)
Benzodiazepine in Prior 60 Days	32244 (15.6%)	30615 (15.5%)	1629 (16.9%)	62 (29.8%)
Non-benzo Hypnotic in Prior 60 Days	16114 (7.8%)	15465 (7.8%)	649 (6.7%)	24 (11.5%)
Gabapentinoid in Prior 60 Days	54158 (26.1%)	51577 (26.1%)	2581 (26.8%)	56 (26.9%)

[1] Categories are not mutually exclusive.
[2] 18,511 missing AUDIT Score and 410 missing BMI.
[3] From ICD-9 and ICD-10 diagnoses in the prior 12 months.
[4] Includes opioid use disorder.

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G

Perspectives from the Department of Veterans Affairs Pain/Opioid Consortium on Research Veteran Engagement Panel

INTRODUCTION

The National Academy of Sciences, Engineering, and Medicine (National Academies) Committee on Evaluating the Effects of Opioids and Benzodiazepines on All-Cause Mortality sought perspectives of veterans who obtained pain care management and treatment from the Veterans Health Administration (VHA). The committee collaborated with the Department of Veterans Affairs (VA) Health Systems Research (HSR) Pain/Opioid Consortium on Research (Pain/Opioid CORE) Veteran Engagement Panel (VEP) to obtain these perspectives. A summary of the input obtained follows.

Background

The Pain/Opioid CORE is one of the four VA HSR-funded COREs. The goal of the COREs is to help and enhance collaborative research to improve care provided to veterans, especially by prioritizing research areas. The Pain/Opioid CORE focuses on research on pain, especially nonpharmacological interventions, opioid prescribing, and opioid use disorder.[1] One aspect of the Pain/Opioid CORE is the VEP, composed of 13 veterans who have experience with chronic pain and/or opioids and help provide guidance to VA researchers from a veteran's perspective.

To help formulate and prepare for the panel discussion, per National Academies policies, National Academies project staff met and provided VEP staff and members with the statement of task, the committee's purpose in hearing from veterans, and how the findings would be shared with the committee and used in the final report. VEP staff sought consent from veterans on the panel on behalf of the National Academies. The National Academies does not provide an honorarium to participants or volunteers. However, these VEP members were compensated for their time through COREs. National Academies staff worked with the committee to develop a focus group discussion facilitation guide, which was shared with the VA Pain/Opioid CORE staff for their approval. After a joint review and approval process, a final guide was approved by the committee and VA Pain/Opioid CORE staff for use during the VEP discussion.

[1] https://www.hsrd.research.va.gov/centers/core (accessed September 17, 2024).

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SUMMARY

VEP staff helped facilitate a panel discussion with eight veterans from the Pain/Opioid CORE VEP: six women and two men who served from the early 1970s to 2015; about half served in the Army, with the remainder serving in the Navy or Air Force.

Several themes emerged through the panel discussion. First, VEP veterans reported that pain management differed by service era. For example, they reported that opioid pharmacotherapy to manage pain was more readily available during the Vietnam campaign, compared to later campaigns, such as post-9/11, when nonopioid medications, such as ibuprofen and acetaminophen, were more readily available. Second, during active duty, veterans were encouraged to shorten their breaks so as to return to active service sooner, especially when staffing was short. Third, continuation of care when transitioning from active duty to post-military care varied, with some veterans reporting a lack of continuity in care. Fourth, opioid prescribing policies changed over time—although prescribing became more restrictive, some panel members noted that pain management shifted toward a participatory process that prioritized joint decision making between provider and veteran. Fifth, multiple VEP veterans mentioned that the Mission Act provided more options for pain management and treatment, especially nonpharmacological strategies, such as acupuncture and physiotherapy. The veterans noted, though, that options varied by VHA facilities, and their availability was not always guaranteed. In addition, the onus of finding providers and obtaining referrals for treatment was often left to the veteran. Sixth, the VEP veterans felt that both VHA and civilian providers often refused to prescribe opioid pharmacotherapy, even when warranted. Veterans reported feeling that they had not been listened to and were inadequately treated to help manage pain. Seventh, they mentioned that many of those prescribing opioid pharmacotherapy were averse to tapering or discontinuation. The veterans reported that these could lead to the following: (a) "provider shopping" to find ones who would be willing to continue to prescribe opioids; (b) turning to nonprescribed alternatives, such as alcohol and cannabis for pain management, especially given easier access to those substances; (c) feeling neglected when experiencing unmanaged pain; and (d) seeking care out of the VHA.

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H

Approach to Data Analysis and Code Library

INTRODUCTION

The following describes the approach to the data analysis conducted by the committee for the following studies: Study 1 (opioid initiation among those with and without current benzodiazepine fill), studies 2a and 2b (opioid baseline, dose escalation), and study 3 (benzodiazepine initiation among those on long-term opioid pharmacotherapy). Westat, the subcontractor, had access to the data and analyzed the data available through outlined sources. All analyses were conducted using SAS 9.4 and SAS Enterprise Guide.

The following describes the data sources used for the analyses, including covariates, and overall approach to constructing the analytic data files.

Data Sources

Per data use agreements with Veterans Health Administration (VHA), Westat obtained access to health record data from VHA CDW and Centers for Medicare & Medicaid Services (CMS) Medicare files. VHA CDW provided a snapshot of medical records in the VA Informatics and Computing Infrastructure (VINCI) workspace, and the database tables within VINCI were linked using unique individual identifiers assigned by the VHA (PatientICN). CMS datafiles were provided in the database as SAS datasets and linked to VHA medical records by Social Security number (SSN). Death data for SSNs in the VINCI extract were obtained from National Death Index files per an internal request to the Joint Department of Veterans Affairs (VA) and Department of Defense Mortality Data Repository Data team and added back to the veteran record using the SSN.

Only the subcontractor had access to personally identifiable health information and personally identifiable information; all access to the data and analyses occurred within the VA firewall and data ecosystems. All analyses were also conducted within the VA firewall, and the final analytic aggregated results were removed from VINCI to provide to the committee only after privacy review. All approved data analysts who worked on this study were also subject to a VA background check, maintained up-to-date human subjects training, and worked within Westat's designated workspace on the server. The National Academies of Sciences, Engineering, and Medicine (National Academies) Institutional Review Board approved the study. Study results do not report data if sample sizes were 10 or fewer individuals. This helps to ensure confidentiality of individuals in the study and is in line with CMS data

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policy and the National Center for Health Statistics (NCHS) recommendations.[1,2] Furthermore, cells are marked as unreliable where sample sizes were 20 or fewer.

Covariates

Prescription data were obtained from both VHA outpatient prescriptions and CMS Medicare provided Part D claims. Drug list lookup tables were used to identify valid opioid prescriptions that were filled (picked up) from the VHA and CMS.

All diagnostic specific covariates were derived using a valid ICD-9 or ICD-10 code from either VHA CDW or CMS files. For example, veterans with an end stage renal disease (ESRD) code in VHA files, CMS files, or both would be coded as having ESRD.

Demographic variables were obtained from VHA. For some demographics, such as age and marital status, the record closest to the veteran study start date was used. Other demographics were based on all records such as sex, race, and ethnicity.

Overall Approach to Analytic Files

Westat obtained records for any patients with an encounter in the VHA between 2005 and 2020. Data extraction, preparation, cleaning, and transformation of the billions of VHA records was necessary to eventually create the final study analysis datasets.

The first data prep step was to identify eligible veterans for the study (i.e., all study groups). Westat applied inclusion and exclusion criteria approved by the National Academies committee along with VHA best practice to drop suspect records (e.g., test cases and bad SSNs). The next step involved identifying veterans prescribed the main drugs of interest at any time, which involved a manual step of reviewing all the VHA drug codes to flag the drugs of interest and then linking that reference file back to the VHA prescription data.

After identifying eligible veterans and an extract on their drug use, a sample frame was created for each of the studies based on the committee criteria (e.g., no drug use before first study month). A veteran may appear multiple times in the sample frame with different episodes of drug use. For study 1, a random episode is retained for each veteran. For study 2, the first episode is retained for each veteran. For study 3, all veteran episodes are retained, given the much smaller sample size for analysis. Using the selected sample, covariates are pulled from the VHA and CMS medical records then assigned in reference to the veteran's first study month in the episode (e.g., veteran age, heart disease in past 12 months) and put into an analytic dataset.

Quality Control Process

Westat followed committee defined protocol to define study specific sample populations and conduct analyses. The lead researcher drafted initial specifications for the programmers to implement based on committee decisions. Iterations of the study protocol were implemented and made with committee consent. Upon completing analysis, Westat drafted results memos to share with the committee that included methodologic and programming notes where appropriate. The lead analyst and programmer wrote the memos, with one serving as the primary writer and the other in a quality control (QC) role. The results were also reviewed by the project director for quality control and privacy review processes.

SAS PROGRAMS:

An extensive number of scripts were written for this study and can be grouped by purpose. Tables H-1 and H-2 contain each script along with its name and purpose.

[1] U.S. Department of Health and Human Services. 2020. *CMS Cell Suppression Policy*. https://www.hhs.gov/guidance/document/cms-cell-suppression-policy (accessed September 19, 2024).

[2] National Center for Health Statistics. 2023. *Underlying Cause of Death 1999-2020*. https://wonder.cdc.gov/wonder/help/ucd.html#Source (accessed August 24, 2024).

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

1) Data Extraction and Transformation—veteran demographics and covariates were extracted from CDW and CMS, and they were saved to SAS datasets to later be used in assembling the analytic datasets. The team manually created ICD and Diagnosis reference files that were used by the scripts
   i. Demographic Variables
   ii. Drug Variables
   iii. Covariates defined by diagnostic codes
      1. Lookup tables
2) Identifying Eligible Veterans
   i. Inclusion/Exclusion
3) Creating Study 1 Analysis Data Sets
   i. Sample Frame
   ii. Random sampling
   iii. Creation of Analytic Files—Linkage of VHA, NDI and CMS files
   iv. Fixes to code—additional derived variables
   v. Main analysis
   vi. Sensitivity Analysis
4) Creating Study 2 Analysis Data Sets
   i. Sample Frame
   ii. Sampling - First eligible episode
   iii. Creation of Analytic Files—Linkage of VHA, NDI and CMS files
   iv. Main analysis
   v. Bootstrap for main analysis to produce confidence intervals
   vi. Sensitivity Analysis
5) Creating Study 3 Analysis Data Sets
   i. Sample Frame
   ii. Sampling
   iii. Creation of Analytic Files—Linkage of VHA, NDI and CMS files
   iv. Main analysis
   v. Sensitivity Analysis

DATA PREPARATION PROGRAMS[3]

Table H-1 Data Preparation Programs

Folder	Program	Purpose
1_Eligible Veterans		
	Define Eligible Gasper Cohort.sas	Clean the CDW Spatient table by removing invalid SSNs, SSNs associated with different PatientICN and vice versa, VeteranFlag = N, test patients, vets deceased before 2006, birth year 1907–2001
2_CDW Extract		
	ADR_Enroll.sas	Extract ADR Enrollment data from CDW
	BMI.sas	Extract vital signs data on height and weight and calculate body mass index
	Ever Demographics.sas	Extract veteran demographics from CDW
	FindDrug_GABAPENTIN.sas	Extract drug prescription data from CDW
	FindDrug_Opioid.sas	Extract drug prescription data from CDW
	FindDrug_RF_032024.sas	
	FindDrugs.sas	Extract drug prescription data from CDW
	Hospice.sas	Identify and extract hospice diagnosis (DX) records from CDW

continued

[3] Note: Study 1 is referred to as trial 1, 4, and 5. Study 2 is referred to as trial 2. Study 3 is referred to as trial 3.

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Table H-1 Continued

Folder	Program	Purpose
	Inpatient Hospital Admission.sas	Identify and extract inpatient hospital admission DX records from CDW
	Insurance.sas	Identify and extract insurance DX records from CDW
	Nonmelanoma Cancer.sas	Identify and extract non-melanoma cancer DX records from CDW
	NursingHomeAdmission.sas	Identify and extract nursing home admission DX records from CDW
	painscore.sas	Extract veteran pain scores from CDW
	preindexDx ICD9.sas	Identify and extract ICD9 DX records from CDW
	preindexDx ICD10.sas	Identify and extract ICD10 DX records from CDW
	preindexDx2 ICD9.sas	Identify and extract ICD9 DX records from CDW for diagnoses where two or more occurrences is of interest
	preindexDx2 ICD10.sas	Identify and extract ICD10 DX records from CDW for diagnoses where two or more occurrences is of interest
	Skin Cancer.sas	Identify and extract skin cancer DX records from CDW
	sleep DX.sas	Identify and extract sleep DX records from CDW
	Trial2 exclusions.sas	
	VA first encounter.sas	Identify and extract veterans first VHA encounter from CDW
	VA_birth_marital.sas	Extract veteran demographics from CDW
	VHA_Drug_Reference_Flags_2_14_24.xlsx	Reference file containing VA drug primary keys (SIDs) with flags to assign them to National Academies drug category
	VHA_Drug_Reference_Flags_2_23_24.xlsx	(UPDATED) Reference file containing VA drug primary keys (SIDs) with flags to assign them to National Academies drug category
	VHA_Drug_Reference_Flags_3_11_24.xlsx	(UPDATED) Reference file containing VA drug primary keys (SIDs) with flags to assign them to National Academies drug category
	VHA_Drug_Reference_Flags_3_20_24.xlsx	(UPDATED) Reference file containing VA drug primary keys (SIDs) with flags to assign them to National Academies drug category

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Table H-1 Continued

Folder	Program	Purpose
3_CMS Extract		
	Add PatientICN to CMS files.sas	Add VA PatientSID identifier to CMS covariate data.
	Add PatientICN to CPT_AcutePainfulInjury.sas	Add VA PatientSID identifier to CMS covariate data.
	Add PatientICN to PalliativeCare_NonMelanomaCancers.sas	Add VA PatientSID identifier to CMS covariate data.
	CMS drug benzo06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_ACETAMIN06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_Antidepressant06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_BUPREN06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_BUSPIRONE06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_CARBAMAZEPINE06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_Confounder06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_FullAgonistOpioid06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_GABAPENTIN06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_HYDROXYZINE06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_Insomnia06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_LIQUID_LAAM06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_LTOT06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_METHADONE06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_Migraine06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_MIRTAZAPINE06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_MuscleRelaxer06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_NALTREXONE06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_nonopioids06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_opioids06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files

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Table H-1 Continued

Folder	Program	Purpose
	CMS drug_OXCARBAZEPINE06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_PartialAgonistOpioid06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_PREGABALIN06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_TOPIRAMATE06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS drug_VENLAFAXINE06_19.sas	Extract drug prescription data from 2006 to 2019 CMS files
	CMS_Drug_Reference_Flags_2_14_24.xlsx	Reference file containing CMS drug names with flags to assign them to National Academies drug category
	CMS_Drug_Reference_Flags_3_20_24.xlsx	Reference file containing CMS drug names with flags to assign them to National Academies drug category
	Add PatientICN to Covariates_7Files.sas	Add VA PatientSID identifier to CMS covariate data.
	Add PatientICN to CovariatesFiles.sas	Add VA PatientSID identifier to CMS covariate data.
	Add PatientICN to Pain_DXFiles.sas	Add VA PatientSID identifier to CMS covariate data.
4_NDI		
	S1. Attach PatientICN to NDI and suicide flag.sas	Attach VA person ID to NDI returned results and create flag identify mortality cause associated with suicide codes
5_Determine Episodes\ Trial 2		
	1. Opioid Episode Sample Frame.sas	To identify eligible episodes for veterans using opioids and create a sample frame.
	2. Find First Episode with MME below 50_20240301.sas	OLD/DEPRECATED—Merge on monthly MME data to veteran episode sample and flag veteran episodes with their baseline monthly MME (opioid dosage) to identify eligible episodes and create descriptive statistics.
	2. Find First Episode with MME below 50_20240301.sas	Merge on monthly MME data to veteran episode sample and flag veteran episodes with their baseline monthly MME (opioid dosage) to identify eligible episodes and create descriptive statistics.
	4. Build Veteran Episode Month Arrays.sas	To build a veteran episode month array for the veteran episodes. Note: Trial 2 did not sample, so a veteran may appear multiple times in analysis datasets.

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Table H-1 Continued

Folder	Program	Purpose
5_Determine Episodes| Trial 3		
	1. Benzo Episode Sample Frame.sas	To identify eligible episodes for veterans using benzodiazepines and create a sample frame.
	2. Insomnia or Antidepressant Episode Sample Frame.sas	To identify eligible episodes for veterans using insomnia or antidepressants and create a sample frame.
	3. Sample Veteran Episodes (Trial3).sas	To identify episodes where veterans used both insomnia and antidepressants, describe the frequency of this, and create a random sample of episodes (later decided to use a census of eligible episodes without sampling)
	4. Build Veteran Episode Month Arrays.sas	To build a veteran episode month array for the sampled veteran episodes
5_Determine Episodes| Trial4 (updated analytic sampling frame but reference Trial 1)		
	1. Opioid Episode Sample Frame.sas	To identify eligible episodes for veterans using opioids and create a sample frame
	2. NonOpioid Episode Sample Frame.sas	To identify eligible episodes for veterans using nonopioids and create a sample frame
	3. Sample Veteran Episodes (Trial4).sas	To identify episodes where veterans used both opioids and nonopioids, describe the frequency of this, and create a random sample of episodes
	4. Build Veteran Episode Month Arrays.sas	To build a veteran episode month array for the sampled veteran episodes
6_Create Data Sets | Trial2		
	0.10 Ever and TM0 Demographics T2.sas	Create analysis dataset containing veteran demographics and covariates related to first month in episode
	0.15 Append new covariates to Demo T2.sas	Add new covariates that the National Academies committee wants to the analysis demographics dataset
	0.20 Time Series T2.sas	Create analysis dataset contain veteran-episode-months and various flags per month
	0.25 Append new covariates to Time Series T2.sas	Add new covariates that the National Academies committee wants to the analysis time series dataset
	0.251 Append new covariates to Time Series T2.sas	Add new covariates that the National Academies committee wants to the analysis time series dataset
	0.252 Append new covariates to Time Series T2.sas	Add new covariates that the National Academies committee wants to the analysis time series dataset

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Table H-1 Continued

Folder	Program	Purpose
	T2_EPISODES_FIRSTUNDER50_MMEs.sas	Construct Trial 2 timeseries opioid MME dataset; examine the result of censoring episodes based on MME values and opioid discontinuation
	1.0 T2 Episodes.sas	OLD/DEPRECATED—This was Chris pointing Sherrie to some MME merging code from 5_Determine Episodes\Trial2\2. Find First Episode with MME below 50_20240301.sas
	1.0 T2 Episodes_V3.sas	Construct flags and outcome measures for T2 analysis dataset in preparation for G-formula macro; censor veteran episodes when they cease opioid use for 3 consecutive months Examine and QC variable distributions
	1.0 T2 Episodes_V4.sas	Update from previous 1.0 T2 Episodes_ V3.sas code file—add/create lagged covariates for benzodiazepine use and pain score from the month before veteran episode baseline
6_Create Data Sets | Trial3		
	0.10 Ever and TM0 Demographics.sas	Create analysis dataset containing veteran demographics and covariates related to first month in episode
	0.15 Append new covariates to Demo T3.sas	Add new covariates that the National Academies committee wants to the analysis demographics dataset
	0.151 Append new covariates to Demo T3.sas	Add new covariates that the National Academies committee wants to the analysis demographics dataset
	0.152 Append new covariates to Demo T3.sas	Add new covariates that the National Academies committee wants to the analysis demographics dataset
	0.20 Time Series T3.sas	Create analysis dataset contain Veteran-Episode-Months and various flags per month
	0.25 Append new covariates to Time Series T3.sas	Add new covariates that the National Academies committee wants to the analysis time series dataset
	1b. NDI Unadjusted Analysis—t3.sas	(QC/Exploratory) Import date and reason of death from NDI dataset to construct outcome measures, examine distribution, and produce preliminary analysis output for QC
	2. Analysis Data.sas	Create final analysis covariates, produce IPTW, reshape data to the episode-month level, create outcome measures, and finalize Trial 3 analysis dataset, output QC materials and descriptive statistics

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Table H-1 Continued

Folder	Program	Purpose
	2. Analysis Data_0709.sas	Update to previous file—2; analysis Data.sas—Episodes with simultaneous initiation of benzodiazepine and insomnia/ antidepressant use excluded
	3. Analysis of Expanded Time Series T3.sas	(UNUSED/Exploratory); exploratory method of removing the overlapping portion of 12-month-duration episodes for upcoming sensitivity analysis
	9a. Adhoc—BenzoSupply in TM0.sas	Ad hoc request to extract benzodiazepine day supply for month TM0
6_Create Data Sets | Trial4 (Trial 1)		
	0.10 Ever and TM0 Demographics.sas	Create analysis dataset containing veteran demographics and covariates related to first month in episode
	0.15 Append new covariates to Demo T4.sas	Add new covariates that the National Academies committee wants to the analysis demographics dataset
	0.151 Append new covariates to Demo T4.sas	Add new covariates that the National Academies committee wants to the analysis demographics dataset
	0.152 Append new covariates to Demo T4.sas	Add new covariates that the National Academies committee wants to the analysis demographics dataset
	0.153 Append new covariates to Demo T4.sas	Add new covariates that the National Academies committee wants to the analysis demographics dataset
	0.20 Time Series.sas	Create analysis dataset contain veteran-episode-months and various flags per month
	0.25 Append new covariates to Time Series T4.sas	Add new covariates that the National Academies committee wants to the analysis time series dataset
	1b. NDI Unadjusted Analysis—t4.sas	(QC/Exploratory) Import date and reason of death from NDI dataset to construct outcome measures, examine distribution, and produce preliminary analysis output for QC
	T4_TimeSeries_MMEs.sas	Construct monthly time series opioid MME dataset for Trial 4 analysis dataset

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Table H-1 Continued

Folder	Program	Purpose
	2. Analysis Data.sas	Beginning from same sample of episodes used in Trial 1, treatment arms are Opioid+Benzo vs. Opioid+NoBenzo; create final analysis covariates, produce IPTW, reshape data to the episode-month level, create outcome measures, and finalize Trial 4 analysis dataset Output QC materials and descriptive statistics
6_Create Data Sets | Trial5 (Additional Update to Trial 4/Trial 1 Specifications)		
	2. Analysis Data.sas	Beginning from same sample of episodes used in Trial 1, treatment arms are Opioid vs. NonOpioid in two stratified cohorts—5a: NonBenzo and 5b: benzo; create final analysis covariates, produce IPTW (per protocol weights are produced in separate monthly slices), reshape data to the episode-month level, create outcome measures, and finalize Trial 5a and 5b analysis datasets, output QC materials and descriptive statistics
9_MME		
	Opioid MME_RF_20240214.sas	Import drug flags and drug strength values, merge onto veteran RX data to calculate monthly opioid MME
	Opioid MME_RF_20240223.sas	(UPDATED) Import drug flags and drug strength values, merge onto veteran RX data to calculate monthly opioid MME
	Opioid MME_RF_20240227.sas	(UPDATED) Import drug flags and drug strength values, merge onto veteran RX data to calculate monthly opioid MME
	CDW Opioid MME_outliers_QC_20240227.sas	(QC) Examine veteran episodes with unreasonable MME values
	Opioid MME_RF_20240304.sas	(UPDATED) Import drug flags and drug strength values, merge onto veteran RX data to calculate monthly opioid MME
	Opioid MME_OutlierEpisodes_20240311.sas	(QC) Examine veteran episodes with unreasonable MME values
	Opioid MME_OutlierDrugs_20240311.sas	(QC) Examine drugs with unreasonable MME values
	Build_Opioid_MME_Lookup_20240318.sas	Construct lookup table of monthly veteran MME dosage used in later dataset construction steps
G-formula (Trial 2)		
	gformula4.0.sas	Download from online
	DeathMainAnalyses_0-20_20-40\	

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Table H-1 Continued

Folder	Program	Purpose
	Gformula_data_derived_FlagVar.sas	derived flags variables
	g_DeathOutcome_allvars_flagb1.sas	with bootstrap (n = 5)
	g_DeathOutcome_allvars_flagb5.sas	with bootstrap (n = 5)
	g_DeathOutcome_allvars_flagb1_V2.sas	
	g_DeathOutcome_allvars_flagb2_V2.sas	
	g_DeathOutcome_allvars_flagb3_V2.sas	
	g_DeathOutcome_allvars_flagb4_V2.sas	
	g_DeathOutcome_allvars_flagb5_V2.sas	
	Opioid MME_OutlierDrugs_20240311.sas	
	DeathSensitivityAnalyses\	
	Gformula_data_derived_FlagVar_SensitivityAnalyses.sas	derived new flags, based on SensitivityAnalyses tables (0–40, 40–50)
	g_DeathOutcome_Sensitivity_flagb1_V2.sas	
	g_DeathOutcome_Sensitivity_flagb2_V2.sas	
	g_DeathOutcome_Sensitivity_flagb3_V2.sas	
	g_DeathOutcome_Sensitivity_flagb4_V2.sas	
	g_DeathOutcome_Sensitivity_flagb5_V2.sas	
	g_DeathOutcome_Sensitivity_flagb1.sas	with bootstrap (n = 5)
	g_DeathOutcome_Sensitivity_flagb2.sas	with bootstrap (n = 5)
	g_DeathOutcome_Sensitivity_flagb3.sas	with bootstrap (n = 5)
	g_DeathOutcome_Sensitivity_flagb4.sas	with bootstrap (n = 5)
	g_DeathOutcome_Sensitivity_flagb5.sas	with bootstrap (n = 5)
	DeathSensitivityAnalyses_flagb3\	
	Gformula_data_derived_FlagVar_SensitivityAnalyses.sas	
	g_DeathOutcome_Sensitivity_flagb1_V2.sas	
	g_DeathOutcome_Sensitivity_flagb2_V2.sas	
	g_DeathOutcome_Sensitivity_flagb3_V2.sas	
	g_DeathOutcome_Sensitivity_flagb4_V2.sas	
	g_DeathOutcome_Sensitivity_flagb5_V2.sas	
	g_DeathOutcome_Sensitivity_flagb1.sas	with bootstrap (n = 5)
	g_DeathOutcome_Sensitivity_flagb2.sas	with bootstrap (n = 5)
	g_DeathOutcome_Sensitivity_flagb3.sas	with bootstrap (n = 5)
	g_DeathOutcome_Sensitivity_flagb4.sas	with bootstrap (n = 5)
	g_DeathOutcome_Sensitivity_flagb5.sas	with bootstrap (n = 5)
	DeathSensitivityAnalyses_flagb3\	based on SensitivityAnalyses tables (0-40, 40-50)

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Table H-1 Continued

Folder	Program	Purpose
	g_Out0_50_flaga6_0_20.sas	Produce estimates and standard errors for 400 bootstrap estimates
	g_Out0_51_flaga6_20_50.sas	
	g_Out0_52_flaga6_40_50.sas	
	g_Out51_100_flaga6_0_20.sas	
	g_Out52_101_flaga6_20_50.sas	
	g_Out53_102_flaga6_40_50.sas	
	g_Out101_150_flaga6_0_20.sas	
	g_Out102_151_flaga6_20_50.sas	
	g_Out103_152_flaga6_40_50.sas	
	g_Out151_200_flaga6_0_20.sas	
	g_Out152_201_flaga6_20_50.sas	
	g_Out153_202_flaga6_40_50.sas	
	g_Out201_250_flaga6_0_20.sas	
	g_Out202_251_flaga6_20_50.sas	
	g_Out203_252_flaga6_40_50.sas	
	g_Out251_300_flaga6_0_20.sas	
	g_Out252_301_flaga6_20_50.sas	
	g_Out253_302_flaga6_40_50.sas	
	g_Out301_350_flaga6_0_20.sas	
	g_Out302_351_flaga6_20_50.sas	
	g_Out303_352_flaga6_40_50.sas	
	g_Out351_400_flaga6_0_20.sas	
	g_Out352_400_flaga6_20_50.sas	
	g_Out353_400_flaga6_40_50.sas	
	g_Out0_53_flag6b_Fast.sas	
	g_Out54_103_flag6b_Fast.sas	
	g_Out104_153_flag6b_Fast.sas	
	g_Out154_203_flag6b_Fast.sas	
	g_Out204_253_flag6b_Fast.sas	
	g_Out254_303_flag6b_Fast.sas	
	g_Out304_353_flag6b_Fast.sas	
	g_Out354_400_flag6b_Fast.sas	
	g_Out0_54_flag6b_Slow.sas	
	g_Out55_104_flag6b_Slow.sas	
	g_Out105_154_flag6b_Slow.sas	
	g_Out155_204_flag6b_Slow.sas	
	g_Out205_254_flag6b_Slow.sas	
	g_Out255_304_flag6b_Slow.sas	
	g_Out305_354_flag6b_Slow.sas	
	g_Out355_400_flag6b_Slow.sas	
	g_Out0_55_flag6b_Stable.sas	
	g_Out56_105_flag6b_Stable.sas	
	g_Out106_155_flag6b_Stable.sas	
	g_Out156_205_flag6b_Stable.sas	
	g_Out206_255_flag6b_Stable.sas	
	g_Out256_305_flag6b_Stable.sas	
	g_Out306_355_flag6b_Stable.sas	
	g_Out356_400_flag6b_Stable.sas	
	g_out_comb_flaga6_0_20.sas	
	g_out_comb_flaga6_40_50.sas	
	g_out_comb_flaga6_20_50.sas	
	g_out_comb_flagb6_Fast.sas	
	g_out_comb_flagb6_Slow.sas	
	g_out_comb_flagb6_Stable.sas	
	g_Sex_Male.sas	

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table H-1 Continued

Folder	Program	Purpose
	g_Sex_Female.sas	
	g_Race_Black.sas	
	g_Race_Asian.sas	
	g_Race_NativeAmerican.sas	
	g_Race_White.sas	
	g_Race_Hawaiian.sas	
	g_Race_Multi.sas	
	g_VHA only.sas	
	g_CMS only.sas	
	g_Dual_bothVHA_CMS.sas	where VA_CMS_flag ="DUAL: both VHA and CMS")
	g_Ethnicity_Hispanic.sas	
	g_Ethnicity_Not_Hispanic.sas	
	g_Age_18_34.sas	
	g_Age_35_54.sas	
	g_Age_55_74.sas	
	g_Age_75_Plus.sas	
	g_Age_0_64.sas	
	g_Age_65_Plus.sas	
	g_StudyYear_2014_2020.sas	
	g_StudyYear_2007_2012.sas	
	g_data_flgOUDdx.sas	Only apply: flgOUDdx=1 and nVEM=0 then delete Censoring: RxMonth=. (3 mons), flgCancer=1 or flgHospice=1
	g_flgOUDdx_Yes.sas	used data only apply RxMonth and (flgCancer or flgHospice); if flgOUDdx=1;
	g_flgOUDdx_No.sas	used data only apply RxMonth and (flgCancer or flgHospice); if flgOUDdx=0;
	g_Ethnicity_Missing.sas	
	Bootstrap\	
	g_DeathOutcome_flaga6_0_20.sas	0-20, flaga6_cat=1, 20-40,flaga6_cat=2, 40-50, flaga6_cat=3
	g_DeathOutcome_flaga6_20_50.sas	'20< MME <= 50'
	g_DeathOutcome_flaga6_40_50	'40< MME <= 50'
	g_DeathOutcome_Sensitivity_flagb6_Fast.sas	Derived flagb6_cat, Trajectory 10-20 Fast, intmax1=2
	g_DeathOutcome_Sensitivity_flagb6_Slow.sas	Derived flagb6_cat, Trajectory 5-10 Slow
	g_DeathOutcome_Sensitivity_flagb6_Stable	Derived flagb6_cat, Trajectory 0-5 Stable
	g_DeathOutcome_Sensitivity_flagb6_Fast_edit.sas	Derived flagb6_cat, Trajectory 10-20 Fast, intmin1=3

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

DATA ANALYSIS PROGRAMS[4]

Table H-2 Data Analysis Programs

Folder	Program	Purpose
7_Analysis		
	Trial 1_ITT.sas	Trial 1 (opioid vs. nonopioid) intent-to-treat (ITT) methodology (no censoring)—death rate, proportional hazard ratio, survival curve, time to discontinuation, cumulative incidence curve
	Trial 1_PerProtocol.sas	Trial 1 (opioid vs. nonopioid) per protocol methodology (censoring based on Rx adherence) – death rate, proportional hazard ratio, survival curve, time to discontinuation, cumulative incidence curve
	Trial 3_ITT.sas	Trial 3 (benzodiazepine vs. insomnia/antidepressant vs. both) ITT methodology (no censoring)—death rate, proportional hazard ratio, survival curve, time to discontinuation, cumulative incidence curve
	Trial 3_ITT_2cat.sas	Trial 3 (benzodiazepine vs. insomnia/antidepressant, with "both" included in benzodiazepine) ITT methodology (no censoring)—death rate, proportional hazard ratio, survival curve, time to discontinuation, cumulative incidence curve
	Trial 3_ITT_update0709.sas	Trial 3 (benzodiazepine vs. insomnia/antidepressant, with "both" excluded from analysis) ITT methodology (no censoring)—death rate, proportional hazard ratio, survival curve, time to discontinuation, cumulative incidence curve
	Trial 3_SA_macro.sas	Trial 3 (benzodiazepine vs. insomnia/antidepressant, with "both" excluded from analysis) ITT methodology (no censoring)—sensitivity analysis groupings, death rates, proportional hazard ratios
	Trial 3_SA_macro_extendedTS.sas	Trial 3 (benzodiazepine vs. insomnia/antidepressant, with "both" excluded from analysis) ITT methodology (no censoring)—sensitivity analysis of 12-month episode duration, death rates, proportional hazard ratios
	Trial 3_SA_macro_min5pill.sas	Trial 3 (benzodiazepine vs. insomnia/antidepressant, with "both" excluded from analysis) ITT methodology (no censoring)—sensitivity analysis of at least five pills for benzodiazepine initiation, death rates, proportional hazard ratios
	Trial 4_ITT.sas	Trial 4 (opioid+benzo vs. opioid+nobenzo) ITT methodology (no censoring)—death rate, proportional hazard ratio, survival curve, time to discontinuation, cumulative incidence curve
	Trial 4_PerProtocol.sas	Trial 4 (opioid+benzo vs. opioid+nobenzo) per protocol methodology (censoring based on Rx adherence)—death rate, proportional hazard ratio, survival curve, time to discontinuation, cumulative incidence curve
	Trial 5_combo.sas	Trial 1a/1b (opioid vs. nonopioid, stratified by benzo/nobenzo) ITT methodology (no censoring)—death rate, proportional hazard ratio, survival curve, time to discontinuation, cumulative incidence curve

[4] Note: Study 1 is referred to as trial 1, 4, and 5. Study 2 is referred to as trial 2. Study 3 is referred to as trial 3.

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

Table H-2 Continued

Folder	Program	Purpose
	Trial 5_PerProtocol.sas	Trial 1a/1b (opioid vs. nonopioid, stratified by benzo/nobenzo) per protocol methodology (censoring based on Rx adherence)—death rate, proportional hazard ratio, survival curve, time to discontinuation, cumulative incidence curve
	Trial1SA_Adhoc—age by insurance.as	Examine crosstabulation of veteran age by type of insurance/health system
	AdHoc—death rate by year.sas	Examine distribution of veteran deaths per year
	SA_macro.sas	Trial 1a/1b (opioid vs. nonopioid, stratified by benzo/nobenzo) per protocol methodology (censoring based on Rx adherence)—Sensitivity Analysis groupings, death rates, proportional hazard ratios
	SA_macro_survcurve.sas	Trial 1a/1b (opioid vs. nonopioid, stratified by benzo/nobenzo) per protocol methodology (censoring based on Rx adherence)—Sensitivity Analysis groupings, survival curve data
	SurvCurvData.sas	Trial 1a/1b (opioid vs. nonopioid, stratified by benzo/nobenzo), survival curve data for both ITT and per protocol
	Bonferroni_p_values.sas	Generate Bonferroni-Holm-adjusted *p*-values due to the multiple tests done through sensitivity analysis
	Truncated_Weight_Rerun_macro_t1.sas	Rerun Trial 1 main and sensitivity analyses with truncated weights (weights <1st% set to 1% value, >99th% set to 99th%)
	Truncated_Weight_Rerun_macro_t3.sas	Rerun Trial 3 main and sensitivity analyses with truncated weights (weights <1st% set to 1% value, >99th% set to 99th%)

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I

Covariate International Classification of Disease Code Table

TABLE I-1 Covariate International Classification of Diseases (ICD) Codes

Health Condition	ICD-9 code	ICD-10 code
Adjustment Disorders + Post-traumatic Stress Disorder	309.81, 308.3, 309.0, 309.89, 309.9, 309.3, 309.4, 309.98, 309.24, 309.28, 309.1, 309.2	F43.10, F43.0, F43.8, F43.9
Alcohol Use Disorder	305, 303, 303.90	F10.10, F10.2, F10.0
Anemia Deficiency	285.9, 282.9, 281.9, 283.9, 285.1, 281.90, 281.91, 281.92, 281.94, 281.99, 283.90, 283.99, 285.90, 285.91, 285.92, 285.93, 285.94, 285.99	D50.1, D50.8, D50.9
Anxiety	293.84, 300.00, 300.01, 300.02, 300.09, 300.10, 300.11, 300.12, 300.13, 300.14, 300.15, 300.16, 300.19, 300.20, 300.21, 300.22, 300.23, 300.29, 300.4, 300.5, 300.6, 300.7, 300.81, 300.82, 300.89, 300.9	F40, F40.0, F40.00, F40.01, F40.02, F40.1, F40.10, F40.11, F40.2, F40.21, F40.210, F40.218, F40.22, F40.220, F40.228, F40.23, F40.230, F40.231, F40.232, F40.233, F40.24, F40.240, F40.241, F40.242, F40.243, F40.248, F40.29, F40.290, F40.291, F40.298, F40.8, F40.9, F41, F41.0, F41.1, F41.3, F41.8, F41.9
Attention Deficit Disorder + Attention Deficit Hyperactivity Disorder	314.01, 314.00	F90.2, F90.0, F90.1, F90.8, F90.9
Bipolar Disorder	296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.50, 296.89, 301.13, 296.80, 296.89, 296.7	F31.0, F31.10, F31.11, F31.12, F31.13, F31.2, F31.30, F31.31, F31.32, F31.4, F31.5, F31.60, F31.61, F31.62, F31.63, F31.64, F31.70, F31.71, F31.72, F31.73, F31.74, F31.75, F31.76, F31.77, F31.78, F31.81, F31.89, F31.9, F34.81, F34.89, F34.1

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
Blood Loss Anemia	280	D50
Cardiovascular Disease	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 410, 410.0, 410.00, 410.01, 410.02, 410.1, 410.10, 410.11, 410.12, 410.2, 410.20, 410.21, 410.3, 410.30, 410.31, 410.32, 410.4, 410.40, 410.41, 410.42, 410.5, 410.50, 410.51, 410.52, 410.6, 410.60, 410.61, 410.62, 410.7, 410.70, 410.71, 410.72, 410.8, 410.80, 410.81, 410.82, 410.9, 410.90, 410.91, 410.92, 411, 411.0, 411.1, 411.8, 411.81, 411.89, 412, 413, 413.0, 413.1, 413.9, 414, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.1, 414.10, 414.11, 414.12, 414.19, 414.2, 414.3, 414.4, 414.8, 414.9, 428, 428.0, 428.1, 428.2, 428.20, 428.21, 428.22, 428.23, 428.3, 428.31, 428.32, 428.33, 428.4, 428.41, 428.42, 428.43, 428.9, 430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 438.1, 438.11, 438.12, 438.13, 438.14, 438.19, 438.2, 438.21, 438.22, 438.3, 438.31, 438.32, 438.4, 438.41, 438.42, 438.5, 438.51, 438.52, 438.53, 438.6, 438.7, 438.8, 438.81, 438.82, 438.83, 438.84, 438.85, 438.89, 438.9	I11.0, I13 0, I13.2, I50.814, I50.9, I50.1, I25.2, I67.89, I60.9, I61.9

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
Cerebrovascular Disease	430, 431, 432, 432.1, 432.9, 433, 433.01, 433.1, 433.11, 433.2, 433.21, 433.3, 433.31, 433.8, 433.81, 433.9, 433.91, 434, 434.01, 434.1, 434.11, 434.9, 434.91, 435, 435.1, 435.2, 435.3, 435.8, 435.9, 436, 437, 437.1, 437.2, 437.3, 437.4, 437.5, 437.6, 437.7, 437.8, 437.9, 438, 438.1, 438.11, 438.12, 438.13, 438.14, 438.19, 438.2, 438.21, 438.22, 438.3, 438.31, 438.32, 438.4, 438.41, 438.42, 438.5, 438.51, 438.52, 438.53, 438.6, 438.7, 438.8, 438.81, 438.82, 438.83, 438.84, 438.85, 438.89, 438.9	I67, I67.0, I67.1, I67.2, I67.3, I67.4, I67.5, I67.6, I67.7, I67.8, I67.81, I67.82, I67.83, I67.84, I67.841, I67.848, I67.85, I67.850, I67.858, I67.89, I67.9, I60, I60.0, I60.00, I60.01, I60.02, I60.1, I60.10, I60.11, I60.12, I60.2, I60.3, I60.30, I60.31, I60.32, I60.4, I60.5, I60.50, I60.51, I60.52, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I62, I62.0, I62.00, I62.01, I62.02, I62.03, I62.1, I62.9, I63, I63.0, I63.00, I63.01, I63.011, I63.012, I63.013, I63.019, I63.02, I63.03, I63.031, I63.032, I63.033, I63.039, I63.09, I63.1, I63.10, I63.11, I63.111, I63.112, I63.113, I63.119, I63.12, I63.13, I63.131, I63.132, I63.133, I63.139, I63.19, I63.2, I63.20, I63.21, I63.211, I63.212, I63.213, I63.219, I63.22, I63.23, I63.231, I63.232, I63.233, I63.239, I63.29, I63.3, I63.30, I63.31, I63.311, I63.312, I63.313, I63.319, I63.32, I63.321, I63.322, I63.323, I63.329, I63.33, I63.331, I63.332, I63.333, I63.339, I63.34, I63.341, I63.342, I63.343, I63.349, I63.39, I63.4, I63.40, I63.41, I63.411, I63.412, I63.413, I63.419, I63.42, I63.421, I63.422, I63.423, I63.429, I63.43, I63.431, I63.432, I63.433, I63.439, I63.44, I63.441, I63.442, I63.443, I63.449, I63.49, I63.5, I63.50, I63.51, I63.511, I63.512, I63.513, I63.519, I63.52, I63.521, I63.522, I63.523, I63.529, I63.53, I63.531, I63.532, I63.533, I63.539, I63.54, I63.541, I63.542, I63.543, I63.549, I63.59, I63.6, I63.8, I63.81, I63.89, I63.9, I65, I65.0, I65.01, I65.02, I65.03, I65.09, I65.1, I65.2, I65.21, I65.22, I65.23, I65.29, I65.8, I65.9, I63, I63.0, I63.00, I63.01, I63.011, I63.012, I63.013, I63.019, I63.02, I63.03, I63.031, I63.032, I63.033, I63.039, I63.09, I63.1, I63.10, I63.11, I63.111, I63.112, I63.113, I63.119, I63.12, I63.13, I63.131, I63.132, I63.133, I63.139, I63.19, I63.2, I63.20, I63.21, I63.211, I63.212, I63.213, I63.219, I63.22, I63.23, I63.231, I63.232, I63.233, I63.239, I63.29, I63.3, I63.30, I63.31, I63.311, I63.312, I63.313, I63.319, I63.32, I63.321, I63.322, I63.323, I63.329, I63.33, I63.331, I63.332, I63.333, I63.339, I63.34, I63.341, I63.342, I63.343, I63.349, I63.39, I63.4, I63.40, I63.41, I63.411, I63.412, I63.413, I63.419, I63.42, I63.421, I63.422, I63.423, I63.429, I63.43, I63.431, I63.432, I63.433, I63.439, I63.44, I63.441, I63.442, I63.443, I63.449, I63.49, I63.5, I63.50, I63.51, I63.511, I63.512, I63.513, I63.519, I63.52, I63.521, I63.522, I63.523, I63.529, I63.53, I63.531, I63.532, I63.533, I63.539, I63.54, I63.541, I63.542, I63.543, I63.549, I63.59, I63.6, I63.8, I63.81, I63.89, I63.9, I68, I68.0, I68.2, I68.8, I69, I69.0, I69.00, I69.01, I69.010, I69.011, I69.012, I69.013, I69.014, I69.015, I69.018, I69.019, I69.02, I69.020, I69.021, I69.022, I69.023, I69.028, I69.03, I69.031, I69.032, I69.033, I69.034, I69.039, I69.04, I69.041, I69.042, I69.043, I69.044, I69.049, I69.05, I69.051, I69.052, I69.053, I69.054, I69.059, I69.06, I69.061, I69.062, I69.063, I69.064, I69.065, I69.069, I69.09, I69.090, I69.091, I69.092, I69.093, I69.098, I69.1, I69.10, I69.11, I69.110, I69.111, I69.112, I69.113, I69.114, I69.115, I69.118, I69.119, I69.12, I69.120, I69.121, I69.122, I69.123, I69.128, I69.13, I69.131, I69.132, I69.133, I69.134, I69.139, I69.14, I69.141, I69.142, I69.143, I69.144, I69.149, I69.15, I69.151, I69.152, I69.153, I69.154, I69.159, I69.16,

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
		I69.161, I69.162, I69.163, I69.164, I69.165, I69.169, I69.19, I69.190, I69.191, I69.192, I69.193, I69.198, I69.2, I69.20, I69.21, I69.210, I69.211, I69.212, I69.213, I69.214, I69.215, I69.218, I69.219, I69.22, I69.220, I69.221, I69.222, I69.223, I69.228, I69.23, I69.231, I69.232, I69.233, I69.234, I69.239, I69.24, I69.241, I69.242, I69.243, I69.244, I69.249, I69.25, I69.251, I69.252, I69.253, I69.254, I69.259, I69.26, I69.261, I69.262, I69.263, I69.264, I69.265, I69.269, I69.29, I69.290, I69.291, I69.292, I69.293, I69.298, I69.3, I69.30, I69.31, I69.310, I69.311, I69.312, I69.313, I69.314, I69.315, I69.318, I69.319, I69.32, I69.320, I69.321, I69.322, I69.323, I69.328, I69.33, I69.331, I69.332, I69.333, I69.334, I69.339, I69.34, I69.341, I69.342, I69.343, I69.344, I69.349, I69.35, I69.351, I69.352, I69.353, I69.354, I69.359, I69.36, I69.361, I69.362, I69.363, I69.364, I69.365, I69.369, I69.39, I69.390, I69.391, I69.392, I69.393, I69.398, I69.8, I69.80, I69.81, I69.810, I69.811, I69.812, I69.813, I69.814, I69.815, I69.818, I69.819, I69.82, I69.820, I69.821, I69.822, I69.823, I69.828, I69.83, I69.831, I69.832, I69.833, I69.834, I69.839, I69.84, I69.841, I69.842, I69.843, I69.844, I69.849, I69.85, I69.851, I69.852, I69.853, I69.854, I69.859, I69.86, I69.861, I69.862, I69.863, I69.864, I69.865, I69.869, I69.89, I69.890, I69.891, I69.892, I69.893, I69.898, I69.9, I69.90, I69.91, I69.910, I69.911, I69.912, I69.913, I69.914, I69.915, I69.918, I69.919, I69.92, I69.920, I69.921, I69.922, I69.923, I69.928, I69.93, I69.931, I69.932, I69.933, I69.934, I69.939, I69.94, I69.941, I69.942, I69.943, I69.944, I69.949, I69.95, I69.951, I69.952, I69.953, I69.954, I69.959, I69.96, I69.961, I69.962, I69.963, I69.964, I69.965, I69.969, I69.99, I69.990, I69.991, I69.992, I69.993, I69.998
Chronic Lung Disease	491.2, 491.21, 491.22, 493.2, 493.2, 493.21, 493.22, 490, 491, 491.1, 492, 492.8, 493, 491.8, 491.9, 493.01, 493.02, 493.1, 493.11, 493.12, 493.81, 493.82, 493.9, 493.91, 493.92, 494, 494.1, 495, 495.1, 495.2, 495.3, 495.4, 495.5, 495.6, 495.7, 495.8, 495.9, 496	J44, J44.0, J44.1, J44.8, J44.81, J44.89, J44.9, J40, J41, J41.0, J41.1, J41.8, J42, J43, J43.0, J43.1, J43.2, J43.8, J43.9, J45, J45.2, J45.20, J45.21, J45.22, J45.3, J45.30, J45.31, J45.32, J45.4, J45.41, J45.40, J45.42, J45.5, J45.50, J45.51, J45.52, J45.9, J45.90, J45.901, J45.902, J45.909, J45.99, J45.990, J45.991, J45.998, J47, J47.0, J47.1, J47.9, J4A, J4A.0, J4A.8, J4A.9
Chronic Obstructive Pulmonary Disease	491.2, 491.21, 491.22, 493.2, 493.21, 493.22	J44, J44.0, J44.1, J44.8, J44.81, J44.89, J44.9
Circadian Rhythm Sleep Disorder	327.3, 327.31, 327.32, 327.33, 327.34, 327.35, 327.36, 327.37, 327.39	G47.2, G47.20, G47.21, G47.22, G47.23, G47.24, G47.25, G47.26, G47.27, G47.29
Cirrhosis	571.2, 571.5, 571.6, 572.3, 572.4, 456.8, 155	K70.2, K70.3, K70.4, K72.1, K74.0, K74.3, K74.4, K74.5, K74.6, K76.6, K76.7, I85.0, I85.9, I98.3, I98.2, I86.4, C22.0

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
Dementia	290, 291.2, 292.82, 294, 331.1, 290.1, 209.1, 290.11, 290.12, 290.13, 290.2, 290.21, 290.3, 290.4, 290.41, 290.42, 290.43, 290.8, 290.9, 294, 294.1, 294.11, 294.2, 294.21, 294.8, 294.9, 331.19, 331.82	F01, F02, F03, F04, F05, F01.5, F01.50, F01.51, F01.511, F01.518, F01.52, F01.53, F01.54, F01.A, F01.A0, F01.A1, F01.A11, F01.A18, F01.A2, F01.A3, F01.A4, F01.B, F01.B1, F01.B11, F01.B18, F01.B2, F01.B3, F01.B4, F01.C, F01.C0, F01.C1, F01.C11, F01.C18, F01.C2, F01.C3, F04.C4, F02, F02.8, F02.80, F02.811, F02.818, F02.82, F02.83, F02.84, F02.A, F02.A0, F02.A1, F02.A11, F02.A18, F02.A2, F02.A3, F02.A4, F02.B, F02.B0, F02.B1, F02.B11, F02.B18, F02.B2, F02.B3, F02.B4, F02.C, F02.C0, F02.C1, F02.C11, F02.C18, F02.C2, F02.C3, F02.C4, F03, F03.9, F03.90, F03.91, F03.911, F03.918, F03.92, F03.93, F03.94, F03.A, F03.A0, F03.A1, F03.A11, F03.A18, F03.A2, F03.F3, F03.A4, F03.B, F03.B1, F03.B11, F03.B18, F03.B2, F03.B3, F03.B4, F03.C, F03.C0, F03.C1, F03.C11, F03.C18, F03.C2, F03.C3, F03.C4
Depression	296.99, 625.4, 293.83, 311, 296.2, 296.22, 296.23, 296.3, 296.32, 296.33, 309.1	F06.31, F06.32, F06.34, F32.81, F32.89, F32.9, N94.3, F32.0, F32, F32.1, F32.2, F32.4, F32.5, F32.8, F32.A
Diabetes	250, 250.01, 250.02, 250.03, 250.1, 250.11, 250.12, 250.13, 250.2, 250.21, 250.22, 250.23, 250.3, 250.31, 250.32, 250.33, 250.4, 250.41, 250.42, 250.43, 250.5, 250.51, 250.52, 250.53, 250.6, 250.61, 250.62, 250.63, 250.7, 250.71, 250.72, 250.73, 250.8, 250.81, 250.82, 250.83, 250.9, 250.91, 250.92, 250.93	E0800, E0801, E0810, E0811, E08618, E08620, E08621, E08622, E08628, E08630, E08638, E08641, E08649, E0865, E0869, E088, E089, E0900, E0901, E0910, E0911, E09618, E09620, E09621, E09622, E09628, E09630, E09638, E09641, E09649, E0965, E0969, E098, E099, E1010, E1011, E10618, E10620, E10621, E10622, E10628, E10630, E10638, E10641, E10649, E1065, E1069, E108, E109, E1100, E1101, E11618, E11620, E11621, E11622, E11628, E11630, E11638, E11641, E11649, E1165, E1169, E118, E119, E1300, E1301, E1310, E1311, E13618, E13620, E13621, E13622, E13628, E13630, E13638, E13641, E13649, E1365, E1369, E138, E139, R81

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
Drug Use Disorder	304.1, 304.11, 304.12, 304.13, 304.2, 304.21, 304.22, 304.23, 304.3, 304.31, 304.32, 304.33, 304.4, 304.41, 304.42, 304.43, 304.5, 304.51, 304.52, 304.53, 304.6, 304.61, 304.62, 304.63, 304.7, 304.71, 304.72, 304.73, 304.8, 304.81, 304.82, 304.83, 304.9, 304.91, 304.92, 304.93	F12, F12.1, F12.10, F12.11, F12.12, F12.120, F12.121, F12.122, F12.129, F12.13, F12.15, F12.150, F12.151, F12.159, F12.18, F12.180, F12.188, F12.19, F12.2, F12.20, F12.21, F12.22, F12.220, F12.221, F12.222, F12.229, F12.23, F12.25, F12.250, F12.251, F12.259, F12.28, F12.280, F12.288, F12.29, F12.9, F12.90, F12.91, F12.92, F12.920, F12.921, F12.922, F12.929, F12.93, F12.95, F12.950, F12.951, F12.959, F12.98, F12.980, F12.988, F12.99, F13, F13.1, F13.10, F13.11, F13.12, F13.120, F13.121, F13.129, F13.13, F13.130, F13.131, F13.132, F13.139, F13.14, F13.15, F13.150, F13.151, F13.159, F13.18, F13.180, F13.181, F13.182, F13.188, F13.19, F13.2, F13.20, F13.21, F13.22, F13.220, F13.221, F13.229, F13.23, F13.230, F13.231, F13.232, F13.239, F13.24, F13.25, F13.250, F13.251, F13.259, F13.26, F13.27, F13.28, F13.280, F13.281, F13.282, F13.288, F13.29, F13.9, F13.90, F13.91, F13.92, F13.920, F13.921, F13.929, F13.93, F13.930, F13.931, F13.932, F13.939, F13.94, F13.95, F13.950, F13.951, F13.959, F13.96, F13.97, F13.98, F13.980, F13.981, F13.982, F13.988, F13.99, F14, F14.1, F14.10, F14.11, F14.12, F14.120, F14.121, F14.122, F14.129, F14.13, F14.14, F14.15, F14.150, F14.151, F14.159, F14.18, F14.180, F14.181, F14.182, F14.188, F14.19, F14.2, F14.20, F14.21, F14.22, F14.220, F14.221, F14.222, F14.229, F14.23, F14.24, F14.25, F14.250, F14.251, F14.259, F14.28, F14.280, F14.281, F14.282, F14.288, F14.29, F14.9, F14.90, F14.91, F14.92, F14.920, F14.921, F14.922, F14.929, F14.93, F14.94, F14.95, F14.950, F14.951, F14.959, F14.98, F14.980, F14.981, F14.982, F14.988, F14.99, F15, F15.1, F15.10, F15.11, F15.12, F15.120, F15.121, F15.122, F15.129, F15.13, F15.14, F15.15, F15.150, F15.151, F15.159, F15.18, F15.180, F15.181, F15.182, F15.188, F15.19, F15.2, F15.20, F15.21, F15.22, F15.220, F15.221, F15.222, F15.229, F15.23, F15.24, F15.25, F15.250, F15.251, F15.259, F15.28, F15.280, F15.281, F15.282, F15.288, F15.29, F15.9, F15.90, F15.91, F15.92, F15.920, F15.921, F15.922, F15.929, F15.93, F15.94, F15.95, F15.950, F15.951, F15.959, F15.98, F15.980, F15.981, F15.982, F15.988, F15.99, F16, F16.1, F16.10, F16.11, F16.12, F16.120, F16.121, F16.122, F16.129, F16.14, F16.15, F16.150, F16.151, F16.159, F16.18, F16.180, F16.183, F16.188, F16.19, F16.2, F16.20, F16.21, F16.22, F16.220, F16.221, F16.229, F16.24, F16.25, F16.250, F16.251, F16.259, F16.28, F16.280, F16.283, F16.288, F16.29, F16.9, F16.90, F16.91, F16.92, F16.920, F16.921, F16.929, F16.94, F16.95, F16.950, F16.951, F16.959, F16.98, F16.980, F16.983, F16.988, F16.99, F18, F18.1, F18.10, F18.11, F18.12, F18.120, F18.121, F18.129, F18.14, F18.15, F18.150, F18.151, F18.159, F18.17, F18.18, F18.180, F18.188, F18.19, F18.2, F18.20, F18.21, F18.22, F18.220, F18.221, F18.229, F18.24, F18.25, F18.250, F18.251, F18.259, F18.27, F18.28, F18.280, F18.288, F18.29, F18.9, F18.90, F18.91, F18.92, F18.920, F18.921, F18.929, F18.94, F18.95, F18.950, F18.951, F18.959, F18.97, F18.98, F18.980, F18.988, F18.99, F19, F19.1, F19.10, F19.11, F19.12, F19.120, F19.121, F19.122, F19.129, F19.13, F19.130, F19.131, F19.132, F19.139,

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
		F19.14, F19.15, F19.150, F19.151, F19.159, F19.16, F19.17, F19.18, F19.180, F19.181, F19.182, F19.188, F19.19, F19.2, F19.20, F19.21, F19.22, F19.220, F19.221, F19.222, F19.229, F19.23, F19.230, F19.231, F19.232, F19.239, F19.24, F19.25, F19.250, F19.251, F19.259, F19.26, F19.27, F19.28, F19.280, F19.281, F19.282, F19.288, F19.29, F19.9, F19.90, F19.91, F19.92, F19.920, F19.921, F19.922, F19.929, F19.93, F19.930, F19.931, F19.932, F19.939, F19.94, F19.95, F19.950, F19.951, F19.959, F19.96, F19.97, F19.98, F19.980, F19.981, F19.982, F19.988, F19.99
End Stage Renal Disease	585.6	N18.6, Z99.2

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
Heart Disease	402.01, 410, 412, 413, 414, 433, 431, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 428.1, 428.2, 428.21, 428.22, 428.23, 428.3, 428.31, 428.32, 428.33, 428.4, 428.41, 428.42, 428.43, 428.9, 410.01, 410.02, 410.1, 410.11, 410.12, 410.2, 410.21, 410.22, 410.3, 410.31, 410.32, 410.4, 410.41, 410.42, 410.5, 410.51, 410.52, 410.6, 410.61, 410.62, 410.7, 410.71, 410.72, 410.8, 410.81, 410.82, 410.9, 410.91, 410.92, 411, 411.1, 411.8, 411.81, 411.89, 413.1, 413.9, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.1, 414.11, 414.12, 414.19, 414.2, 414.3, 414.4, 414.8, 414.9, 433, 433.01, 433.1, 433.11, 433.2, 433.21, 433.3, 433.31, 433.8, 433.81, 433.9, 433.91, 434, 434.01, 434.1, 434.11, 434.9, 434.91, 433.01, 433.11, 433.91, 434.01, 434.11, 434.91, 436, 438, 438.11, 438.19, 438.2, 438.21, 438.22, 438.41, 438.5, 438.6, 438.81, 438.82, 438.84, 438.89, 438.9	I50, I50.1, I50.2, I50.20, I50.21, I50.22, I50.23, I50.3, I50.30, I50.31, I50.32, I50.33, I50.4, I50.40, I50.41, I50.42, I50.43, I50.8, I50.81, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9, I11.0, I25.2, I61.9, I13.0, I13.2, I21.09, I21, I21.0 ST, I21.01 ST, I21.02 ST, I21.09 ST, I21.1 ST, I21.11 ST, I21.19 ST, I21.2 ST, I21.21 ST, I21.29 ST, I21.3 ST, I21.4, I21.9, I21.A, I21.A1, I21.A9, I21.B, I20.0, I63.59, I63.30, I63, I63.0, I63.00, I63.01, I63.011, I63.012, I63.013, I63.019, I63.02, I63.03, I63.031, I63.032, I63.033, I63.039, I63.09, I63.1, I63.10, I63.11, I63.111, I63.112, I63.113, I63.119, I63.12, I63.13, I63.131, I63.132, I63.133, I63.139, I63.19, I63.2, I63.20, I63.21, I63.211, I63.212, I63.213, I63.219, I63.22, I63.23, I63.231, I63.232, I63.233, I63.239, I63.29, I63.3, I63.30, I63.31, I63.311, I63.312, I63.313, I63.319, I63.32, I63.321, I63.322, I63.323, I63.329, I63.33, I63.331, I63.332, I63.333, I63.339, I63.34, I63.341, I63.342, I63.343, I63.349, I63.39, I63.4, I63.40, I63.41, I63.411, I63.412, I63.413, I63.419, I63.42, I63.421, I63.422, I63.423, I63.429, I63.43, I63.431, I63.432, I63.433, I63.439, I63.44, I63.441, I63.442, I63.443, I63.449, I63.49, I63.5, I63.50, I63.51, I63.511, I63.512, I63.513, I63.519, I63.52, I63.521, I63.522, I63.523, I63.529, I63.53, I63.531, I63.532, I63.533, I63.539, I63.54, I63.541, I63.542, I63.543, I63.549, I63.59, I63.6, I63.8, I63.81, I63.89, I63.9, I69.920, I67.89, I67.9, I67.858, I69, I69.0, I69.00, I69.01, I69.010, I69.011, I69.012, I69.013, I69.014, I69.015, I69.018, I69.019, I69.02, I69.020, I69.021, I69.022, I69.023, I69.028, I69.03, I69.031, I69.032, I69.033, I69.034, I69.039, I69.04, I69.041, I69.042, I69.043, I69.044, I69.049, I69.05, I69.051, I69.052, I69.053, I69.054, I69.059, I69.06, I69.061, I69.062, I69.063, I69.064, I69.065, I69.069, I69.09, I69.090, I69.091, I69.092, I69.093, I69.098, I69.1, I69.10, I69.11, I69.110, I69.111, I69.112, I69.113, I69.114, I69.115, I69.118, I69.119, I69.12, I69.120, I69.121, I69.122, I69.123, I69.128, I69.13, I69.131, I69.132, I69.133, I69.134, I69.139, I69.14, I69.141, I69.142, I69.143, I69.144, I69.149, I69.15, I69.151, I69.152, I69.153, I69.154, I69.159, I69.16, I69.161, I69.162, I69.163, I69.164, I69.165, I69.169, I69.19, I69.190, I69.191, I69.192, I69.193, I69.198, I69.2, I69.20, I69.21, I69.210, I69.211, I69.212, I69.213, I69.214, I69.215, I69.218, I69.219, I69.22, I69.220, I69.221, I69.222, I69.223, I69.228, I69.23, I69.231, I69.232, I69.233, I69.234, I69.239, I69.24, I69.241, I69.242, I69.243, I69.244, I69.249, I69.25, I69.251, I69.252, I69.253, I69.254, I69.259, I69.26, I69.261, I69.262, I69.263, I69.264, I69.265, I69.269, I69.29, I69.290, I69.291, I69.292, I69.293, I69.298, I69.3, I69.30, I69.31, I69.310, I69.311, I69.312, I69.313, I69.314, I69.315, I69.318, I69.319, I69.32, I69.320, I69.321, I69.322, I69.323, I69.328, I69.33, I69.331, I69.332, I69.333, I69.334, I69.339, I69.34, I69.341, I69.342, I69.343, I69.344, I69.349, I69.35, I69.351, I69.352, I69.353, I69.354, I69.359, I69.36, I69.361, I69.362, I69.363, I69.364, I69.365, I69.369, I69.39, I69.390, I69.391, I69.392, I69.393, I69.398, I69.8, I69.80, I69.81, I69.810, I69.811,

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
		I69.812, I69.813, I69.814, I69.815, I69.818, I69.819, I69.82, I69.820, I69.821, I69.822, I69.823, I69.828, I69.83, I69.831, I69.832, I69.833, I69.834, I69.839, I69.84, I69.841, I69.842, I69.843, I69.844, I69.849, I69.85, I69.851, I69.852, I69.853, I69.854, I69.859, I69.86, I69.861, I69.862, I69.863, I69.864, I69.865, I69.869, I69.89, I69.890, I69.891, I69.892, I69.893, I69.898, I69.9, I69.90, I69.91, I69.910, I69.911, I69.912, I69.913, I69.914, I69.915, I69.918, I69.919, I69.92, I69.920, I69.921, I69.922, I69.923, I69.928, I69.93, I69.931, I69.932, I69.933, I69.934, I69.939, I69.94, I69.941, I69.942, I69.943, I69.944, I69.949, I69.95, I69.951, I69.952, I69.953, I69.954, I69.959, I69.96, I69.961, I69.962, I69.963, I69.964, I69.965, I69.969, I69.99, I69.990, I69.991, I69.992, I69.993, I69.998
Hepatitis C	70.54, 70.7	B17.1, B18.2, B17.0, B17.10, B17.11, B17.2, B17.8, B17.9, B19.2, B19.20, B19.21
HIV and AIDS	042, 042.0, 042.1, 042.2, 042.9	B20.0, B20.2, B20.4, B20.6, B21.0, B21.2, B22.0, B22.2, B24, B20, B20.3
Homelessness	V60.0	Z59.0, Z59.00, Z59.01, Z59.02
Hypersomnia	327.1, 327.11, 327.12, 327.13, 327.14, 327.15, 327.19	G47.1, G47.10, G47.11, G47.12, G47.13, G47.14, G47.19
Insomnia	327.8, 307.48, 307.41, 307.42, 780.52, 327.00	F51.0, F51.01, F51.02, F51.03, F51.04, F51.05, F51.09, F51.1, F51.11, F51.12, F51.13, F51.19
Isolated Symptoms, Apparently Normal Variants, and Unresolved Issues	307.49, 786.09, 307.47, 781.01	F51.8, R06.83, R06.00, R06.09, R06.3, R06.89
Liver Disease	571, 571.1, 571.2, 571.3, 571.4, 571.41, 571.42, 571.49, 571.5, 571.6, 571.8, 571.9, 570, 572, 572.1, 572.2, 572.3, 572.4, 572.8, 573, 573.1, 573.2, 573.3, 573.4, 573.5, 573.8, 573.9	K70, K70.0, K70.1, K70.10, K70.11, K70.2, K70.3, K70.30, K70.31, K70.4, K70.40, K70.41, K70.9, K71, K71.0, K71.1, K71.10, K71.11, K71.2, K71.3, K71.4, K71.5, K71.50, K71.51, K71.6, K71.7, K71.8, K71.9, K72, K72.0, K72.00, K72.01, K72.1, K72.11, K72.10, K72.9, K72.90, K72.91, K73.0, K73, K73.1, K73.2, K73.8, K73.9, K74, K74.0, K74.00, K74.01, K74.02, K74.1, K74.2, K74.3, K74.4, K74.5, K74.6, K74.60, K74.69, K75, K75.0, K75.1, K75.2, K75.3, K75.4, K75.8, K75.81, K75.89, K75.9, K76, K76.0, K76.1, K76.2, K76.3, K76.4, K76.5, K76.6, K76.7, K76.8, K76.81, K76.82, K76.89, K76.9, K77

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
Migraine	346, 346.1, 346.7, 346.2, 346.8, 346.9, 343.3, 346.4	G43, G43.0, G43.00, G43.001, G43.009, G43.01, G43.011, G43.019, G43.1, G43.10, G43.101, G43.109, G43.11, G43.111, G43.119, G43.4, G43.40, G43.401, G43.409, G43.41, G43.411, G43.419, G43.5, G43.50, G43.501, G43.509, G43.51, G43.511, G43.519, G43.6, G43.60, G43.601, G43.609, G43.61, G43.611, G43.619, G43.7, G43.70, G43.701, G43.709, G43.71, G43.711, G43.719, G43.A, G43.A0, G43.A1, G43.B, G43.B0, G43.B1, G43.C, G43.C0, G43.C1, G43.D, G43.D0, G43.D1, G43.8, G43.80, G43.801, G43.809, G43.81, G43.811, G43.819, G43.82, G43.821, G43.829, G43.83, G43.831, G43.839, G43.9, G43.90, G43.901, G43.909, G43.91, G43.911, G43.919, G43.E, G43.E0, G43.E01, G43.E09, G43.E1, G43.E11, G43.E19
Obsessive Compulsive Disorder	300.3	F42
Obstructive Sleep Apnea	327.23	G47.33
Opioid Use Disorder	304, 304.01, 304.02, 304.03, 304.7, 304.71, 304.72, 304.73, 305.5, 305.51, 305.52, 305.53	F11.10, F11.120, F11.121, F11.122, F11.129, F11.14, F11.150, F11.151, F11.159, F11.181, F11.182, F11.188, F11.19, F11.20, F11.21, F11.220, F11.221, F11.222, F11.229, F11.23, F11.24, F11.250, F11.251, F11.259, F11.281, F11.282, F11.288, F11.29, F11.11, F11.13
Other Sleep Disorder	327.8	G47.8, G47.9
Paraplegia	344.1, 344.9, 344.2, 342.9, 344.89, 344.3, 344.31, 344.32, 344.89, 342.9, 438.2, 438.21, 438.22, 438.3, 438.31, 438.32, 438.4, 438.41, 438.42, 438.5, 438.52, 438.51, 438.53, 438.6	G81, G81.0, G81.00, G81.01, G80.02, G81.03, G81.04, G81.1, G81.10, G81.11, G81.12, G81.13, G81.14, G81.9, G81.90, G81.91, G81.92, G81.93, G81.94, G82, G82.2, G82.20, G82.21, G82.22, G82.5, G82.50, G82.51, G82.52, G82.53, G82.54
Parasomnia	327.4, 327.41, 327.42, 327.43, 327.44, 327.49	G47.5, G47.50, G47.51, G47.52, G47.53, G47.54, G47.59
Peptic Ulcer Disease	533.9, 533.90, 533, 533.01, 533.1, 533.11, 533.2, 533.21, 533.3, 533.31, 533.32, 533.4, 533.41, 533.5, 533.51, 533.6, 533.61, 533.7, 533.71, 533.91	K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9
Peripheral Vascular Disease	443.9, 443, 443.1, 443.2, 443.22, 443.23, 443.24, 443.29, 443.8, 443.81, 443.82, 443.89	I73, I73.0, I73.00, I73.01, I73.1, I73.8, I73.81, I73.89, I73.9, I77.72, I77.74, I77.75, I77.76, I77.77, I77.79, I77.8, I77.81
Pulmonary Vascular Disease	417, 417.1, 417.8, 417.9	I26, I26.0, I26.01, I26.02, I26.09, I26.9, I26.90, I26.92, I26.93, I26.94, I26.99, I27, I27.0, I27.1, I27.2, I27.20, I27.21, I27.22, I27.23, I27.24, I27.29, I27.8, I27.81, I27.82, I27.83, I27.89, I27.9, I28, I28.0, I28.1, I28.8, I28.9
Renal Disease	585.9, 585.1, 585, 585.2, 585.3, 585.4, 585.5, 585.6	N18, N18.1, N18.2, N18.3, N18.30, N18.31, N18.32, N18.4, N18.5, N18.6, N18.9, N19

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
Rheumatic Disease	95.6, 95.7, 98.5, 98.51, 98.52, 98.53, 98.59, 99.3, 136.1, 274, 274.01, 274.02, 274.03, 274.1, 274.11, 274.19, 274.8, 274.81, 274.82, 274.89, 274.9, 277.2, 287, 287.1, 287.2, 287.3, 287.31, 287.32, 287.33, 287.39, 287.4, 287.41, 287.49, 287.5, 287.8, 287.9, 344.6, 353, 353.1, 353.2, 353.3, 353.4, 353.5, 353.6, 353.7, 353.8, 353.9, 354, 354.1, 354.2, 354.3, 354.4, 354.5, 354.8, 354.9, 355.5, 357.1, 390, 391, 391.1, 391.2, 391.8, 391.9, 437.4, 443, 443.1, 443.2, 443.21, 443.22, 443.23, 443.24, 443.29, 443.8, 443.81, 443.82, 443.89, 443.9, 446, 446.1, 446.2, 446.21, 446.29, 446.3, 446.4, 446.5, 446.6, 446.7, 447.6, 696, 696.1, 696.2, 696.3, 696.4, 696.5, 696.8, 710, 710.1, 710.2, 710.3, 710.4, 710.5, 710.8, 710.9, 711, 711.01, 711.02, 711.03, 711.04, 711.05, 711.06, 711.07, 711.08, 711.09, 711.1, 711.11, 711.12, 711.13, 711.14, 711.15, 711.16, 711.17, 711.18, 711.19, 711.2, 711.21, 711.22, 711.23, 711.24, 711.25, 711.26, 711.27, 711.28, 711.29, 711.3, 711.31, 711.32, 711.33, 711.34, 711.35, 711.36, 711.37, 711.38, 711.39, 711.4, 711.41, 711.42, 711.43, 711.44, 711.45, 711.46, 711.47, 711.48, 711.49, 711.5, 711.51, 711.52, 711.53, 711.54, 711.55, 711.56, 711.57, 711.58, 711.59, 711.6, 711.61, 711.62, 711.63, 711.64, 711.65, 711.66, 711.67, 711.68, 711.69, 711.7, 711.71, 711.72, 711.73, 711.74, 711.75, 711.76, 711.77, 711.78, 711.79, 711.8, 711.81, 711.82, 711.83, 711.84, 711.85, 711.86, 711.87, 711.88, 711.89, 711.9, 711.91, 711.92, 711.93, 711.94, 711.95, 711.96, 711.97, 711.98, 711.99, 712, 712.1, 712.11, 712.12, 712.13, 712.14, 712.15, 712.16, 712.17, 712.18, 712.19, 712.2, 712.21, 712.22, 712.23, 712.24, 712.25, 712.26, 712.27, 712.28, 712.29, 712.3, 712.31, 712.32, 712.33, 712.34, 712.35, 712.36, 712.37, 712.38, 712.39, 712.8, 712.81, 712.82, 712.83, 712.84, 712.85, 712.86, 712.87, 712.88, 712.89, 712.9, 712.91, 712.92, 712.93, 712.94, 712.95, 712.96, 712.97, 712.98, 712.99, 713, 713.1, 713.2, 713.3, 713.4, 713.5, 713.6, 713.7, 713.8, 714, 714.1, 714.2, 714.3, 714.3, 714.31, 714.32, 714.33, 714.4, 714.8, 714.81, 714.89, 714.9, 715, 715.04, 715.09, 715.1, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.2, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.3, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.8, 715.89, 715.9, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 716, 716.1, 716.11, 716.12, 716.13, 716.14, 716.15, 716.16, 716.17, 716.18, 716.19, 716.2, 716.2, 716.21, 716.22, 716.23, 716.24, 716.25, 716.26, 716.27, 716.28, 716.29, 716.3, 716.31, 716.32, 716.33, 716.34, 716.35, 716.36, 716.37, 716.38, 716.39, 716.6, 716.61, 716.62, 716.63, 716.64, 716.65, 716.66, 716.67, 716.68, 716.8, 716.81,	A01.04, A02.23, A18.02, A39.83, A39.84, A54.42, A69.23, B06.82, B26.85, B42.82, D68.62, D86, D86.0, D86.1, D86.2, D86.3, D86.8, D86.89, D86.9, E78.81, E79.0, G98.0, H01.12, H01.121, H01.122, H01.123, H01.124, H01.125, H01.126, H01.129, H44.11, H44.111, H44.112, H44.113, H44.119, H44.13, H44.131, H44.132, H44.133, H44.139, L40, L40.0, L40.1, L40.2, L40.3, L40.4, L40.5, L40.50, L40.51, L40.52, L40.53, L40.54, L40.59, L40.8, L40.9, L41.0, L41.1, L41.3, L41.4, L93, L93.0, L93.1, L93.2, L94.0, L94.1, M00, M00.0, M00.00, M00.01, M00.011, M00.012, M00.019, M00.02, M00.021, M00.022, M00.029, M00.03, M00.031, M00.032, M00.039, M00.04, M00.041, M00.042, M00.049, M00.05, M00.051, M00.052, M00.059, M00.06, M00.061, M00.062, M00.069, M00.07, M00.071, M00.072, M00.079, M00.08, M00.09, M00.1, M00.10, M00.11, M00.111, M00.112, M00.119, M00.12, M00.121, M00.122, M00.129, M00.13, M00.131, M00.132, M00.139, M00.14, M00.141, M00.142, M00.149, M00.15, M00.151, M00.152, M00.159, M00.16, M00.161, M00.162, M00.169, M00.17, M00.171, M00.172, M00.179, M00.18, M00.19, M00.2, M00.20, M00.21, M00.211, M00.212, M00.219, M00.22, M00.221, M00.222, M00.229, M00.23, M00.231, M00.232, M00.239, M00.24, M00.241, M00.242, M00.249, M00.25, M00.251, M00.252, M00.259, M00.26, M00.261, M00.262, M00.269, M00.27, M00.271, M00.272, M00.279, M00.28, M00.29, M00.8, M00.80, M00.81, M00.811, M00.812, M00.819, M00.82, M00.821, M00.822, M00.829, M00.83, M00.831, M00.832, M00.839, M00.84, M00.841, M00.842, M00.849, M00.85, M00.851, M00.852, M00.859, M00.86, M00.861, M00.862, M00.869, M00.87, M00.871, M00.872, M00.879, M00.88, M00.89, M00.9, M05, M05.0, M05.00, M05.01, M05.011, M05.012, M05.019, M05.02, M05.021, M05.022, M05.029, M05.03, M05.031, M05.032, M05.039, M05.04, M05.041, M05.042, M05.049, M05.05, M05.051, M05.052, M05.059, M05.06, M05.061, M05.062, M05.069, M05.07, M05.071, M05.072, M05.079, M05.09, M05.1, M05.10, M05.11, M05.111, M05.112, M05.119, M05.12, M05.121, M05.122, M05.129, M05.13, M05.131, M05.132, M05.139, M05.14, M05.141, M05.142, M05.149, M05.15, M05.151, M05.152, M05.159, M05.16, M05.161, M05.162, M05.169, M05.17, M05.171, M05.172, M05.179, M05.19, M05.2, M05.20, M05.21, M05.211, M05.212, M05.219, M05.22, M05.221, M05.222, M05.229, M05.23, M05.231, M05.232, M05.239, M05.24, M05.241, M05.242, M05.249, M05.25, M05.251, M05.252, M05.259, M05.26, M05.261, M05.262, M05.269, M05.27, M05.271, M05.272, M05.279, M05.29, M05.3, M05.30, M05.31, M05.311, M05.312, M05.319, M05.32, M05.321, M05.322, M05.329, M05.33, M05.331, M05.332, M05.339, M05.34, M05.341, M05.342, M05.349, M05.35, M05.351, M05.352, M05.359, M05.36, M05.361, M05.362, M05.369, M05.37, M05.371, M05.372, M05.379, M05.39, M05.4, M05.40, M05.41, M05.411, M05.412, M05.419, M05.42, M05.421, M05.422, M05.429, M05.43, M05.431, M05.432, M05.439, M05.44, M05.441, M05.442, M05.449, M05.45, M05.451, M05.452, M05.459, M05.46, M05.461, M05.462, M05.469, M05.47, M05.471, M05.472, M05.479, M05.49, M05.5, M05.50, M05.51, M05.511, M05.512, M05.519,

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
	716.82, 716.83, 716.84, 716.85, 716.86, 716.87, 716.88, 716.89, 716.9, 716.91, 716.92, 716.93, 716.94, 716.95, 716.96, 716.97, 716.98, 716.99, 719, 719.01, 719.02, 719.03, 719.04, 719.05, 719.06, 719.07, 719.08, 719.09, 719.2, 719.4, 719.41, 719.42, 719.43, 719.44, 719.45, 719.46, 719.47, 719.48, 719.49, 719.5, 719.51, 719.52, 719.53, 719.54, 719.55, 719.56, 719.57, 719.58, 719.59, 719.6, 719.61, 719.62, 719.63, 719.64, 719.65, 719.66, 719.67, 719.68, 719.69, 719.7, 719.8, 719.81, 719.82, 719.83, 719.84, 719.85, 719.86, 719.87, 719.88, 719.89, 719.9, 719.91, 719.92, 719.93, 719.94, 719.95, 719.96, 719.97, 719.98, 719.99, 720, 720.1, 720.2, 720.8, 720.81, 720.89, 720.9, 721, 721.1, 721.2, 721.3, 721.4, 721.41, 721.42, 721.5, 721.6, 721.7, 721.8, 721.9, 721.91, 725, 726, 726.1, 726.11, 726.12, 726.13, 726.19, 726.2, 726.3, 726.31, 726.32, 726.33, 726.39, 726.4, 726.5, 726.6, 726.61, 726.62, 726.63, 726.64, 726.65, 726.69, 726.7, 726.71, 726.72, 726.73, 726.79, 726.8, 726.9, 726.91, 727, 727.01, 727.02, 727.03, 727.04, 727.05, 727.06, 727.09, 727.1, 727.2, 727.3, 727.4, 727.41, 727.42, 727.43, 727.49, 727.5, 727.51, 727.59, 727.6, 727.61, 727.62, 727.63, 727.64, 727.65, 727.66, 727.67, 727.68, 727.69, 727.8, 727.81, 727.82, 727.83, 727.89, 727.9, 728, 728.1, 728.11, 728.12, 728.13, 728.19, 728.2, 728.3, 728.6, 728.7, 728.71, 728.79, 728.8, 728.81, 728.82, 728.83, 728.84, 728.85, 728.86, 728.87, 728.88, 728.89, 728.9, 729, 729.1, 729.2, 729.3, 729.31, 729.39, 729.4, 729.5, 729.6, 729.7, 729.71, 729.72, 729.73, 729.79, 729.8, 729.81, 729.82, 729.89, 729.9, 729.91, 729.92, 729.99	M05.52, M05.521, M05.522, M05.529, M05.53, M05.531, M05.532, M05.539, M05.54, M05.541, M05.542, M05.549, M05.55, M05.551, M05.552, M05.559, M05.56, M05.561, M05.562, M05.569, M05.57, M05.571, M05.572, M05.579, M05.59, M05.6, M05.60, M05.61, M05.611, M05.612, M05.619, M05.62, M05.621, M05.622, M05.629, M05.63, M05.631, M05.632, M05.639, M05.64, M05.641, M05.642, M05.649, M05.65, M05.651, M05.652, M05.659, M05.66, M05.661, M05.662, M05.669, M05.67, M05.671, M05.672, M05.679, M05.69, M05.7, M05.70, M05.71, M05.711, M05.712, M05.719, M05.72, M05.721, M05.722, M05.729, M05.73, M05.731, M05.732, M05.739, M05.74, M05.741, M05.742, M05.749, M05.75, M05.751, M05.752, M05.759, M05.76, M05.761, M05.762, M05.769, M05.77, M05.771, M05.772, M05.779, M05.79, M05.8, M05.80, M05.81, M05.811, M05.812, M05.819, M05.82, M05.821, M05.822, M05.829, M05.83, M05.831, M05.832, M05.839, M05.84, M05.841, M05.842, M05.849, M05.85, M05.851, M05.852, M05.859, M05.86, M05.861, M05.862, M05.869, M05.87, M05.871, M05.872, M05.879, M05.89, M05.9, M06, M06.0, M06.00, M06.01, M06.011, M06.012, M06.019, M06.02, M06.021, M06.022, M06.029, M06.03, M06.031, M06.032, M06.039, M06.04, M06.041, M06.042, M06.049, M06.05, M06.051, M06.052, M06.059, M06.06, M06.061, M06.062, M06.069, M06.07, M06.071, M06.072, M06.079, M06.08, M06.09, M06.1, M06.2, M06.20, M06.21, M06.211, M06.212, M06.219, M06.22, M06.221, M06.222, M06.229, M06.23, M06.231, M06.232, M06.239, M06.24, M06.241, M06.242, M06.249, M06.25, M06.251, M06.252, M06.259, M06.26, M06.261, M06.262, M06.269, M06.27, M06.271, M06.272, M06.279, M06.28, M06.29, M06.3, M06.30, M06.31, M06.311, M06.312, M06.319, M06.32, M06.321, M06.322, M06.329, M06.33, M06.331, M06.332, M06.339, M06.34, M06.341, M06.342, M06.349, M06.35, M06.351, M06.352, M06.359, M06.36, M06.361, M06.362, M06.369, M06.37, M06.371, M06.372, M06.379, M06.38, M06.39, M06.4, M06.8, M06.80, M06.81, M06.811, M06.812, M06.819, M06.82, M06.821, M06.822, M06.829, M06.83, M06.831, M06.832, M06.839, M06.84, M06.841, M06.842, M06.849, M06.85, M06.851, M06.852, M06.859, M06.86, M06.861, M06.862, M06.869, M06.87, M06.871, M06.872, M06.879, M06.88, M06.89, M06.9, M08, M08.0, M08.00, M08.01, M08.011, M08.012, M08.019, M08.02, M08.021, M08.022, M08.029, M08.03, M08.031, M08.032, M08.039, M08.04, M08.041, M08.042, M08.049, M08.05, M08.051, M08.052, M08.059, M08.06, M08.061, M08.062, M08.069, M08.07, M08.071, M08.072, M08.079, M08.08, M08.09, M08.1, M08.2, M08.20, M08.21, M08.211, M08.212, M08.219, M08.22, M08.221, M08.222, M08.229, M08.23, M08.231, M08.232, M08.239, M08.24, M08.241, M08.242, M08.249, M08.25, M08.251, M08.252, M08.259, M08.26, M08.261, M08.262, M08.269, M08.27, M08.271, M08.272, M08.279, M08.28, M08.29, M08.3, M08.4, M08.40, M08.41, M08.411, M08.412, M08.419, M08.42, M08.421, M08.422, M08.429, M08.43, M08.431, M08.432, M08.439, M08.44, M08.441, M08.442, M08.449, M08.45, M08.451, M08.452, M08.459, M08.46, M08.461, M08.462, M08.469, M08.47, M08.471, M08.472, M08.479, M08.48,

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
		M08.8, M08.80, M08.81, M08.811, M08.812, M08.819, M08.82, M08.821, M08.822, M08.829, M08.83, M08.831, M08.832, M08.839, M08.84, M08.841, M08.842, M08.849, M08.85, M08.851, M08.852, M08.859, M08.86, M08.861, M08.862, M08.869, M08.87, M08.871, M08.872, M08.879, M08.88, M08.89, M08.9, M08.90, M08.91, M08.911, M08.912, M08.919, M08.92, M08.921, M08.922, M08.929, M08.93, M08.931, M08.932, M08.939, M08.94, M08.941, M08.942, M08.949, M08.95, M08.951, M08.952, M08.959, M08.96, M08.961, M08.962, M08.969, M08.97, M08.971, M08.972, M08.979, M08.98, M08.99, M10, M10.0, M10.00, M10.01, M10.011, M10.012, M10.019, M10.02, M10.021, M10.022, M10.029, M10.03, M10.031, M10.032, M10.039, M10.04, M10.041, M10.042, M10.049, M10.05, M10.051, M10.052, M10.059, M10.06, M10.061, M10.062, M10.069, M10.07, M10.071, M10.072, M10.079, M10.08, M10.09, M10.1, M10.10, M10.11, M10.111, M10.112, M10.119, M10.12, M10.121, M10.122, M10.129, M10.13, M10.131, M10.132, M10.139, M10.14, M10.141, M10.142, M10.149, M10.15, M10.151, M10.152, M10.159, M10.16, M10.161, M10.162, M10.169, M10.17, M10.171, M10.172, M10.179, M10.18, M10.19, M10.2, M10.20, M10.21, M10.211, M10.212, M10.219, M10.22, M10.221, M10.222, M10.229, M10.23, M10.231, M10.232, M10.239, M10.24, M10.241, M10.242, M10.249, M10.25, M10.251, M10.252, M10.259, M10.26, M10.261, M10.262, M10.269, M10.27, M10.271, M10.272, M10.279, M10.28, M10.29, M10.3, M10.30, M10.31, M10.311, M10.312, M10.319, M10.32, M10.321, M10.322, M10.329, M10.33, M10.331, M10.332, M10.339, M10.34, M10.341, M10.342, M10.349, M10.35, M10.351, M10.352, M10.359, M10.36, M10.361, M10.362, M10.369, M10.37, M10.371, M10.372, M10.379, M10.38, M10.39, M10.4, M10.40, M10.41, M10.411, M10.412, M10.419, M10.42, M10.421, M10.422, M10.429, M10.43, M10.431, M10.432, M10.439, M10.44, M10.441, M10.442, M10.449, M10.45, M10.451, M10.452, M10.459, M10.46, M10.461, M10.462, M10.469, M10.47, M10.471, M10.472, M10.479, M10.48, M10.49, M10.9, M13, M13.0, M13.1, M13.10, M13.11, M13.111, M13.112, M13.119, M13.12, M13.121, M13.122, M13.129, M13.13, M13.131, M13.132, M13.139, M13.14, M13.141, M13.142, M13.149, M13.15, M13.151, M13.152, M13.159, M13.16, M13.161, M13.162, M13.169, M13.17, M13.171, M13.172, M13.179, M13.8, M13.80, M13.81, M13.811, M13.812, M13.819, M13.82, M13.821, M13.822, M13.829, M13.83, M13.831, M13.832, M13.839, M13.84, M13.841, M13.842, M13.849, M13.85, M13.851, M13.852, M13.859, M13.86, M13.861, M13.862, M13.869, M13.87, M13.871, M13.872, M13.879, M13.88, M13.89, M15, M15.0, M15.3, M15.4, M15.8, M15.9, M16, M16.0, M16.1, M16.10, M16.11, M16.12, M16.2, M16.3, M16.30, M16.31, M16.32, M16.4, M16.5, M16.50, M16.51, M16.52, M16.6, M16.7, M16.9, M17, M17.0, M17.1, M17.10, M17.11, M17.12, M17.2, M17.3, M17.30, M17.31, M17.32, M17.4, M17.5, M17.9, M18, M18.0, M18.1, M18.10, M18.11, M18.12, M18.2, M18.3, M18.30, M18.31, M18.32, M18.4, M18.5, M18.50, M18.51, M18.52, M18.9, M19, M19.0, M19.01, M19.011, M19.012, M19.019, M19.02, M19.021, M19.022, M19.029, M19.03,

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
		M19.031, M19.032, M19.039, M19.04, M19.041, M19.042, M19.049, M19.07, M19.071, M19.072, M19.079, M19.1, M19.11, M19.111, M19.112, M19.119, M19.12, M19.121, M19.122, M19.129, M19.13, M19.131, M19.132, M19.139, M19.14, M19.141, M19.142, M19.149, M19.17, M19.171, M19.172, M19.179, M19.2, M19.21, M19.211, M19.212, M19.219, M19.22, M19.221, M19.222, M19.229, M19.23, M19.231, M19.232, M19.239, M19.24, M19.241, M19.242, M19.249, M19.27, M19.271, M19.272, M19.279, M19.9, M19.90, M19.91, M19.92, M19.93, M1A, M1A.0, M1A.00, M1A.00X0, M1A.00X1, M1A.01, M1A.011, M1A.0110, M1A.0111, M1A.012, M1A.0120, M1A.0121, M1A.019, M1A.0190, M1A.0191, M1A.02, M1A.021, M1A.0210, M1A.0211, M1A.022, M1A.0220, M1A.0221, M1A.029, M1A.0290, M1A.0291, M1A.03, M1A.031, M1A.0310, M1A.0311, M1A.032, M1A.0320, M1A.0321, M1A.039, M1A.0390, M1A.0391, M1A.04, M1A.041, M1A.0410, M1A.0411, M1A.042, M1A.0420, M1A.0421, M1A.049, M1A.0490, M1A.0491, M1A.05, M1A.051, M1A.0510, M1A.0511, M1A.052, M1A.0520, M1A.0521, M1A.059, M1A.0590, M1A.0591, M1A.06, M1A.061, M1A.0610, M1A.0611, M1A.062, M1A.0620, M1A.0621, M1A.069, M1A.0690, M1A.0691, M1A.07, M1A.071, M1A.0710, M1A.0711, M1A.072, M1A.0720, M1A.0721, M1A.079, M1A.0790, M1A.0791, M1A.08, M1A.08X0, M1A.08X1, M1A.09, M1A.09X0, M1A.09X1, M1A.1, M1A.10, M1A.10X0, M1A.10X1, M1A.11, M1A.111, M1A.1110, M1A.1111, M1A.112, M1A.1120, M1A.1121, M1A.119, M1A.1190, M1A.1191, M1A.12, M1A.121, M1A.1210, M1A.1211, M1A.122, M1A.1220, M1A.1221, M1A.129, M1A.1290, M1A.1291, M1A.13, M1A.131, M1A.1310, M1A.1311, M1A.132, M1A.1320, M1A.1321, M1A.139, M1A.1390, M1A.1391, M1A.14, M1A.141, M1A.1410, M1A.1411, M1A.142, M1A.1420, M1A.1421, M1A.149, M1A.1490, M1A.1491, M1A.15, M1A.151, M1A.1510, M1A.1511, M1A.152, M1A.1520, M1A.1521, M1A.159, M1A.1590, M1A.1591, M1A.16, M1A.161, M1A.1610, M1A.1611, M1A.162, M1A.1620, M1A.1621, M1A.169, M1A.1690, M1A.1691, M1A.17, M1A.171, M1A.1710, M1A.1711, M1A.172, M1A.1720, M1A.1721, M1A.179, M1A.1790, M1A.1791, M1A.18, M1A.18X0, M1A.18X1, M1A.19, M1A.19X0, M1A.19X1, M1A.2, M1A.20, M1A.20X0, M1A.20X1, M1A.21, M1A.211, M1A.2110, M1A.2111, M1A.212, M1A.2120, M1A.2121, M1A.219, M1A.2190, M1A.2191, M1A.22, M1A.221, M1A.2210, M1A.2211, M1A.222, M1A.2220, M1A.2221, M1A.229, M1A.2290, M1A.2291, M1A.23, M1A.231, M1A.2310, M1A.2311, M1A.232, M1A.2320, M1A.2321, M1A.239, M1A.2390, M1A.2391, M1A.24, M1A.241, M1A.2410, M1A.2411, M1A.242, M1A.2420, M1A.2421, M1A.249, M1A.2490, M1A.2491, M1A.25, M1A.251, M1A.2510, M1A.2511, M1A.252, M1A.2520, M1A.2521, M1A.259, M1A.2590, M1A.2591, M1A.26, M1A.261, M1A.2610, M1A.2611, M1A.262, M1A.2620, M1A.2621, M1A.269, M1A.2690, M1A.2691, M1A.27, M1A.271, M1A.2710, M1A.2711, M1A.272, M1A.2720, M1A.2721, M1A.279, M1A.2790, M1A.2791, M1A.28, M1A.28X0, M1A.28X1, M1A.29, M1A.29X0, M1A.29X1, M1A.3, M1A.30,

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
		M1A.30X0, M1A.30X1, M1A.31, M1A.311, M1A.3110, M1A.3111, M1A.312, M1A.3120, M1A.3121, M1A.319, M1A.3190, M1A.3191, M1A.32, M1A.321, M1A.3210, M1A.3211, M1A.322, M1A.3220, M1A.3221, M1A.329, M1A.3290, M1A.3291, M1A.33, M1A.331, M1A.3310, M1A.3311, M1A.332, M1A.3320, M1A.3321, M1A.339, M1A.3390, M1A.3391, M1A.34, M1A.341, M1A.3410, M1A.3411, M1A.342, M1A.3420, M1A.3421, M1A.349, M1A.3490, M1A.3491, M1A.35, M1A.351, M1A.3510, M1A.3511, M1A.352, M1A.3520, M1A.3521, M1A.359, M1A.3590, M1A.3591, M1A.36, M1A.361, M1A.3610, M1A.3611, M1A.362, M1A.3620, M1A.3621, M1A.369, M1A.3690, M1A.3691, M1A.37, M1A.371, M1A.3710, M1A.3711, M1A.372, M1A.3720, M1A.3721, M1A.379, M1A.3790, M1A.3791, M1A.38, M1A.38X0, M1A.38X1, M1A.39, M1A.39X0, M1A.39X1, M1A.4, M1A.40, M1A.40X0, M1A.40X1, M1A.41, M1A.411, M1A.4110, M1A.4111, M1A.412, M1A.4120, M1A.4121, M1A.419, M1A.4190, M1A.4191, M1A.42, M1A.421, M1A.4210, M1A.4211, M1A.422, M1A.4220, M1A.4221, M1A.429, M1A.4290, M1A.4291, M1A.43, M1A.431, M1A.4310, M1A.4311, M1A.432, M1A.4320, M1A.4321, M1A.439, M1A.4390, M1A.4391, M1A.44, M1A.441, M1A.4410, M1A.4411, M1A.442, M1A.4420, M1A.4421, M1A.449, M1A.4490, M1A.4491, M1A.45, M1A.451, M1A.4510, M1A.4511, M1A.452, M1A.4520, M1A.4521, M1A.459, M1A.4590, M1A.4591, M1A.46, M1A.461, M1A.4610, M1A.4611, M1A.462, M1A.4620, M1A.4621, M1A.469, M1A.4690, M1A.4691, M1A.47, M1A.471, M1A.4710, M1A.4711, M1A.472, M1A.4720, M1A.4721, M1A.479, M1A.4790, M1A.4791, M1A.48, M1A.48X0, M1A.48X1, M1A.49, M1A.49X0, M1A.49X1, M1A.9, M1A.9XX0, M1A.9XX1, M32, M32.0, M32.1, M32.10, M32.11, M32.12, M32.13, M32.14, M32.15, M32.19, M32.8, M32.9, M33, M33.0, M33.00, M33.01, M33.02, M33.09, M33.1, M33.10, M33.11, M33.12, M33.19, M33.2, M33.20, M33.21, M33.22, M33.29, M33.9, M33.90, M33.91, M33.92, M33.99, M34, M45, M45.0, M45.1, M45.2, M45.3, M45.4, M45.5, M45.6, M45.7, M45.8, M45.9, M45.A, M45.A0, M45.A1, M45.A2, M45.A3, M45.A4, M45.A5, M45.A6, M45.A7, M45.A8, M45.AB, M46, M46.0, M46.00, M46.01, M46.02, M46.03, M46.04, M46.05, M46.06, M46.07, M46.08, M46.09, M46.1, M46.2, M46.20, M46.21, M46.22, M46.23, M46.24, M46.25, M46.26, M46.27, M46.28, M46.3, M46.30, M46.31, M46.32, M46.33, M46.34, M46.35, M46.36, M46.37, M46.38, M46.39, M46.4, M46.40, M46.41, M46.42, M46.43, M46.44, M46.45, M46.46, M46.47, M46.48, M46.49, M46.5, M46.50, M46.51, M46.52, M46.53, M46.54, M46.55, M46.56, M46.57, M46.58, M46.59, M46.8, M46.80, M46.81, M46.82, M46.83, M46.84, M46.85, M46.86, M46.87, M46.88, M46.89, M46.9, M46.90, M46.91, M46.92, M46.93, M46.94, M46.95, M46.96, M46.97, M46.98, M46.99, M77.2, M77.20, M77.21, M77.22

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
Schizophrenia and Psychotic Disorders	297.1, 298.8, 295.90, 295.70, 298.9	F20.0, F20.1, F20.2, F20.3, F20.5, F20.81, F20.89, F20.9, F21, F22, F23, F24, F25.0, F25.1, F25.8, F25.9, F28, F29
Sleep Disorders Associated with Conditions Classifiable Elsewhere	46.8, 729.1, 345, 784, 530.1, 411.8, 787.2	A81.8, M79.7, G40.5, R51, K21.9, I25.6, R13.1
Sleep Related Movement Disorders	327.5, 327.51, 327.52, 327.53, 327.59	G47.6, G47.61, G47.62, G47.63, G47.69
Suicidal Ideation	V62.84	R45.851
Syncope	780.2	R55
Tobacco Use	305.1, 305.10, 305.11, 305.12, 305.13	F17.200, F17.201, F17.203, F17.208, F17.209, F17.210, F17.211, F17.213, F17.218, F17.219, F17.220, F17.221, F17.223, F17.228, F17.229, F17.290, F17.291, F17.293, F17.298, F17.299, O99.330, O99.331, O99.332, O99.333, O99.334, O99.335, T65.211, T65.212, T65.213, T65.214, T65.221, T65.222, T65.223, T65.224, T65.291, T65.292, T65.293, T65.294, Z71.6, Z72.0, Z87.891, T65.211A, T65.212A, T65.213A, T65.214A, T65.211D, T65.212D, T65.213D, T65.214D, T65.211S, T65.212S, T65.213S, T65.214S, T65.221A, T65.222A, T65.223A, T65.224A, T65.221D, T65.222D, T65.223D, T65.224D, T65.221S, T65.222S, T65.223S, T65.224S, T65.291A, T65.292A, T65.293A, T65.294A, T65.291D, T65.292D, T65.293D, T65.294D, T65.291S, T65.292S, T65.293S, T65.294S

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
Traumatic Brain Injury	959.01, 995.55, 800, 800.01, 800.02, 800.03, 800.04, 800.05, 800.06, 800.09, 800.1, 800.11, 800.12, 800.13, 800.14, 800.15, 800.16, 800.19, 800.2, 800.21, 800.22, 800.23, 800.24, 800.25, 800.26, 800.29, 800.3, 800.31, 800.32, 800.33, 800.34, 800.35, 800.36, 800.39, 800.4, 800.41, 800.42, 800.43, 800.44, 800.45, 800.46, 800.49, 800.5, 800.51, 800.52, 800.53, 800.54, 800.55, 800.56, 800.59, 800.6, 800.61, 800.62, 800.63, 800.64, 800.65, 800.66, 800.69, 800.7, 800.71, 800.72, 800.73, 800.74, 800.75, 800.76, 800.79, 800.8, 800.81, 800.82, 800.83, 800.84, 800.85, 800.86, 800.89, 800.9, 800.91, 800.92, 800.93, 800.94, 800.95, 800.96, 800.99, 801, 801.01, 801.02, 801.03, 801.04, 801.05, 801.06, 801.09, 801.1, 801.11, 801.12, 801.13, 801.14, 801.15, 801.16, 801.19, 801.2, 801.21, 801.22, 801.23, 801.24, 801.25, 801.26, 801.29, 801.3, 801.31, 801.32, 801.33, 801.34, 801.35, 801.36, 801.39, 801.4, 801.41, 801.42, 801.43, 801.44, 801.45, 801.46, 801.49, 801.5, 801.51, 801.52, 801.53, 801.54, 801.55, 801.56, 801.59, 801.6, 801.61, 801.62, 801.63, 801.64, 801.65, 801.66, 801.69, 801.7, 801.71, 801.72, 801.73, 801.74, 801.75, 801.76, 801.79, 801.8, 801.81, 801.82, 801.83, 801.84, 801.85, 801.86, 801.89, 801.9, 801.91, 801.92, 801.93, 801.94, 801.95, 801.96, 801.99, 803, 803.01, 803.02, 803.03, 803.04, 803.05, 803.06, 803.09, 803.1, 803.11, 803.12, 803.13, 803.14, 803.15, 803.16, 803.19, 803.2, 803.21, 803.22, 803.23, 803.24, 803.25, 803.26, 803.29, 803.3, 803.31, 803.32, 803.33, 803.34, 803.35, 803.36, 803.39, 803.4, 803.41, 803.42, 803.43, 803.44, 803.45, 803.46, 803.49, 803.5, 803.51, 803.52, 803.53, 803.54, 803.55, 803.56, 803.59, 803.6, 803.61, 803.62, 803.63, 803.64, 803.65, 803.66, 803.69, 803.7, 803.71, 803.72, 803.73, 803.74, 803.75, 803.76, 803.79, 803.8, 803.81, 803.82, 803.83, 803.84, 803.85, 803.86, 803.89, 803.9, 803.91, 803.92, 803.93, 803.94, 803.95, 803.96, 803.99, 804, 804.01, 804.02, 804.03, 804.04, 804.05, 804.06, 804.09, 804.1, 804.11, 804.12, 804.13, 804.14, 804.15, 804.16, 804.19, 804.2, 804.21, 804.22, 804.23, 804.24, 804.25, 804.26, 804.29, 804.3, 804.31, 804.32, 804.33, 804.34, 804.35, 804.36, 804.39, 804.4, 804.41, 804.42, 804.43, 804.44, 804.45, 804.46, 804.49, 804.5, 804.51, 804.52, 804.53, 804.54, 804.55, 804.56, 804.59, 804.6, 804.61, 804.62, 804.63, 804.64, 804.65, 804.66, 804.69, 804.7, 804.71, 804.72, 804.73, 804.74, 804.75, 804.76, 804.79, 804.8, 804.81, 804.82, 804.83, 804.84, 804.85, 804.86, 804.89, 804.9, 804.91, 804.92, 804.93, 804.94, 804.95, 804.96, 804.99, 850, 850.1, 850.11, 850.12, 850.2, 850.3, 850.4, 850.5, 850.9, 851, 851.01, 851.02, 851.03, 851.04, 851.05, 851.06, 851.09, 851.1, 851.11, 851.12, 851.13, 851.14, 851.15, 851.16, 851.19, 851.2,	S02.0XXA, S02.0XXB, S02.0XXD, S02.0XXG, S02.0XXK, S02.0XXS, S02.1, S06.0, S06.1, S06.2, S06.30, S06.31, S06.32, S06.33, S09.x, R45.0, R45.4, R45.87, R45.86, R45.3, R45.89, R41.840, R41.841, R41.842, R41.843, R41.844, R41.89, G44.301, G44.309, G44.321, G44.329, R42, R43.0, R43.8, R47.82, R47.81, R56.1, S02.10, S02.101, S02.101A, S02.101B, S02.101D, S02.101G, S02.101K, S02.101S, S02.102, S02.102A, S02.102B, S02.102D, S02.102G, S02.102K, S02.102S, S02.109, S02.109A, S02.109B, S02.109D, S02.109G, S02.109K, S02.109S, S02.11, S02.110, S02.110A, S02.110B, S02.110D, S02.110G, S02.110K, S02.110S, S02.111, S02.111A, S02.111B, S02.111D, S02.111G, S02.111K, S02.111S, S02.112, S02.112A, S02.112B, S02.112D, S02.112G, S02.112K, S02.112S, S02.113, S02.113A, S02.113B, S02.113D, S02.113G, S02.113K, S02.113S, S02.118, S02.118A, S02.118B, S02.118D, S02.118G, S02.118K, S02.118S, S02.119, S02.119A, S02.119B, S02.119D, S02.119G, S02.119K, S02.119S, S02.11A, S02.11AA, S02.11AB, S02.11AD, S02.11AG, S02.11AK, S02.11AS, S02.11B, S02.11BA, S02.11BB, S02.11BD, S02.11BG, S02.11BK, S02.11BS, S02.11C, S02.11CA, S02.11CB, S02.11CD, S02.11CG, S02.11CK, S02.11CS, S02.11D, S02.11DA, S02.11DB, S02.11DD, S02.11DG, S02.11DK, S02.11DS, S02.11E, S02.11EA, S02.11EB, S02.11ED, S02.11EG, S02.11EK, S02.11ES, S02.11F, S02.11FA, S02.11FB, S02.11FD, S02.11FG, S02.11FK, S02.11FS, S02.11G, S02.11GA, S02.11GB, S02.11GD, S02.11GG, S02.11GK, S02.11GS, S02.11H, S02.11HA, S02.11HB, S02.11HD, S02.11HG, S02.11HK, S02.11HS, S02.12, S02.121, S02.121A, S02.121B, S02.121D, S02.121G, S02.121K, S02.121S, S02.122, S02.122A, S02.122B, S02.122D, S02.122G, S02.122K, S02.122S, S02.129, S02.129A, S02.129B, S02.129D, S02.129G, S02.129K, S02.129S, S02.19, S02.19XA, S02.19XB, S02.19XD, S02.19XG, S02.19XK, S02.19XS, S02.60, S02.600, S02.600A, S02.600B, S02.600D, S02.600G, S02.600K, S02.600S, S02.601, S02.601A, S02.601B, S02.601D, S02.601G, S02.601K, S02.601S, S02.602, S02.602A, S02.602B, S02.602D, S02.602G, S02.602K, S02.602S, S02.609, S02.609A, S02.609B, S02.609D, S02.609G, S02.609K, S02.609S, S02.61, S02.610, S02.610A, S02.610B, S02.610D, S02.610G, S02.610K, S02.610S, S02.611, S02.611A, S02.611B, S02.611D, S02.611G, S02.611K, S02.611S, S02.612, S02.612A, S02.612B, S02.612D, S02.612G, S02.612K, S02.612S, S02.62, S02.620, S02.620A, S02.620B, S02.620D, S02.620G, S02.620K, S02.620S, S02.621, S02.621A, S02.621B, S02.621D, S02.621G, S02.621K, S02.621S, S02.622, S02.622A, S02.622B, S02.622D, S02.622G, S02.622K, S02.622S, S02.63, S02.630, S02.630A, S02.630B, S02.630D, S02.630G, S02.630K, S02.630S, S02.631, S02.631A, S02.631B, S02.631D, S02.631G, S02.631K, S02.631S, S02.632, S02.632A, S02.632B, S02.632D, S02.632G, S02.632K, S02.632S, S02.9, S02.91, S02.91XA, S02.91XB, S02.91XD, S02.91XG, S02.91XK, S02.91XS, S02.92, S02.92XA, S02.92XB, S02.92XD, S02.92XG, S02.92XK, S02.92XS

continued

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Veterans, Prescription Opioids and Benzodiazepines, and Mortality, 2007–2019: Three Target Trial Emulations

TABLE I-1 Continued

Health Condition	ICD-9 code	ICD-10 code
	851.21, 851.22, 851.23, 851.24, 851.25, 851.26, 851.29, 851.3, 851.31, 851.32, 851.33, 851.34, 851.35, 851.36, 851.39, 851.4, 851.41, 851.42, 851.43, 851.44, 851.45, 851.46, 851.49, 851.5, 851.51, 851.52, 851.53, 851.54, 851.55, 851.56, 851.59, 851.6, 851.61, 851.62, 851.63, 851.64, 851.65, 851.66, 851.69, 851.7, 851.71, 851.72, 851.73, 851.74, 851.75, 851.76, 851.79, 851.8, 851.81, 851.82, 851.83, 851.84, 851.85, 851.86, 851.89, 851.9, 851.91, 851.92, 851.93, 851.94, 851.95, 851.96, 851.99, 852, 852.01, 852.02, 852.03, 852.04, 852.05, 852.06, 852.09, 852.1, 852.11, 852.12, 852.13, 852.14, 852.15, 852.16, 852.19, 852.2, 852.21, 852.22, 852.23, 852.24, 852.25, 852.26, 852.29, 852.3, 852.31, 852.32, 852.33, 852.34, 852.35, 852.36, 852.39, 852.4, 852.41, 852.42, 852.43, 852.44, 852.45, 852.46, 852.49, 852.5, 852.51, 852.52, 852.53, 852.54, 852.55, 852.56, 852.59, 853, 853.01, 853.02, 853.03, 853.04, 853.05, 853.06, 853.09, 853.1, 853.11, 853.12, 853.13, 853.14, 853.15, 853.16, 853.19, 854, 854.01, 854.02, 854.03, 854.04, 854.05, 854.06, 854.09, 854.1, 854.11, 854.12, 854.13, 854.14, 854.15, 854.16, 854.19, 950.1, 950.2, 950.3	

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