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Article

Impacts of an Opioid Safety Initiative on US Veterans Undergoing Cancer Treatment

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Abstract

Background: There is limited research on how the opioid epidemic and consequent risk reduction policies have affected pain management among cancer patients. The purpose of this study was to analyze how the Opioid Safety Initiative (OSI) implemented at the Veterans Health Administration affected opioid prescribing patterns and opioid-related toxicity.
Methods: We performed an interrupted time series analysis of 42 064 opioid-naïve patients treated at the Veterans Health Administration for prostate, lung, breast, and colorectal cancer from 2011 to 2016. Segmented regression was used to evaluate the impact of the OSI on the incidence of any new opioid prescriptions, high-risk prescriptions, persistent use, and pain-related emergency department (ED) visits. We compared the cumulative incidence of adverse opioid events including an opioid-related admission or diagnosis of misuse before and after the OSI. All statistical tests were 2-sided. **Results:** The incidence of new opioid prescriptions was 26.7% (95% confidence interval [CI] = 25.0% to 28.4%) in 2011 and increased to 50.6% (95% CI = 48.3% to 53.0%) by 2013 before OSI implementation (monthly rate of change: +3.3%, 95% CI = 1.3% to 4.2%, $P < .001$). After the OSI, there was a decrease in the monthly rate of change for new prescriptions (−3.4%, 95% CI = −3.9 to −2.9%, $P < .001$). The implementation of the OSI was associated with a decrease in the monthly rate of change of concomitant benzodiazepines and opioid prescriptions (−2.5%, 95% CI = −3.2% to −1.8%, $P < .001$), no statistically significant change in high-dose opioids (−1.2%, 95% CI = −3.2% to 0.9%, $P = .26$), a decrease in persistent opioid use (−5.7%, 95% CI = −6.8% to −4.7%, $P < .001$), and an increase in pain-related ED visits (+3.0%, 95% CI = 1.0% to 5.0%, $P = .003$). The OSI was associated with a decreased incidence of opioid-related admissions (3-year cumulative incidence: 0.9% [95% CI = 0.7% to 1.0%] vs 0.5% [95% CI = 0.4% to 0.6%], $P < .001$) and no statistically significant change in the incidence of opioid misuse (3-year cumulative incidence: 1.2% [95% CI = 1.0% to 1.3%] vs 1.2% [95% CI = 1.1% to 1.4%], $P = .77$). **Conclusions:** The OSI was associated with a relative decline in the rate of new, persistent, and certain high-risk opioid prescribing as well as a slight increase in the rate of pain-related ED visits. Further research on patient-centered outcomes is required to optimize opioid prescribing policies for patients with cancer.

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Rates of opioid-related toxicity and mortality rose throughout the 2000s and 2010s in the United States (1,2). In response to the opioid epidemic, national and health-care system initiatives were developed to curb inappropriate opioid use and reduce the risk of adverse outcomes (3,4). To what degree the opioid epidemic and consequent risk reduction strategies have affected opioid prescribing or toxicity among patients with cancer is not well understood (5,6).

Prescription opioid analgesics remain an often irreplaceable first-line treatment for moderate to severe pain in patients with cancer (7,8). More than two-thirds of patients diagnosed with cancer will survive beyond 5 years, and risks associated

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with opioid analgesics must be considered. It is generally accepted, however, that opioid requirements differ from the noncancer population because of the high prevalence of pain in patients diagnosed with cancer (7,9,10). Accordingly, patients undergoing active cancer treatment are explicitly omitted from general opioid treatment guidelines because of the unique considerations among this population (6,11). Prior studies have demonstrated a reduction in opioid prescribing and toxicity with government or institutional programs in noncancer populations (4,12,13). To ensure that pain is being safely and effectively addressed in cancer patients, it is important to understand the effect of opioid policies and regulations among this distinct population (14).

In October 2013, the Veterans Health Administration (VHA) launched the Opioid Safety Initiative (OSI) to curb high-risk opioid prescribing (3,12,15). The VHA is the largest integrated health system in the United States and serves a population at increased risk for opioid-related adverse effects (16,17). The OSI involved multiple strategies to address high-risk opioid prescribing, including monitoring and reporting patient-, prescriber-, and facility-level prescription patterns (Table 1). A computerized "dashboard" was developed for facility leaders to audit and provide feedback to prescribers. Providers were educated on safe and effective opioid use, and the access to nonpharmacological treatment options was expanded. The program focused on curbing key high-risk prescriptions, including high daily morphine milligram equivalent (MME) doses and concomitant benzodiazepine prescriptions (3). We hypothesized that the OSI would result in a decrease of new opioid prescriptions for patients undergoing cancer treatment.

The purpose of this study was to evaluate the impact of the OSI on patients undergoing definitive cancer treatment. We used an interrupted time series design to evaluate the change in rates of new opioid, high-dose opioid, and concomitant opioid and benzodiazepine prescriptions among opioid-naïve cancer patients. To assess downstream effects of the OSI, we also analyzed the patient-centered outcomes of persistent opioid use, future diagnoses of opioid use disorder, pain-related emergency department (ED) visits, and opioid-related admissions.

Methods

Data Source and Patient Selection

This observational cohort study evaluated patients treated through the VHA using the VA Informatics and Computing Infrastructure database (18). Patient and treatment information were obtained from cancer registry data and International Classification of Disease 9 and 10 codes, as previously described (19). Outpatient prescription data were obtained from the VHA's Pharmacy Benefits Management service. Waivers of consent and authorization were granted by the Research and Development Committee of the VA Health Care System.

Opioid-naïve VHA patients undergoing definitive local treatment for prostate, breast, lung, or colorectal cancer from January 2011 to December 2016 were included. Opioid naïve was defined as no opioid prescriptions from 1 to 12 months before diagnosis (19-22). Patients were excluded if they had metastatic cancer or unknown stage at diagnosis.

Covariates, Exposures, and Outcomes

In October 2013, the VA launched the system-wide OSI to address increasing opioid overuse and toxicity (3). A program dashboard aggregated patient-, clinician-, and facility-level data on opioid prescribing, including high-risk prescriptions such as high daily opioid doses (defined as ≥100 MME) and concomitant benzodiazepine prescriptions (Table 1) (12,19). To guide safer prescribing, providers were alerted to prescribing patterns identified as high risk or deviated from the institutional standard of care.

The primary outcome of this study was the incidence of new opioid prescriptions during the diagnosis treatment window defined as 1 month before to 3 months post the date of first treatment (19,23). Secondary outcomes included rates of high daily dose (≥100 MME) and concomitant benzodiazepine prescriptions during the same diagnosis-treatment window. Longer-term secondary outcomes included persistent opioid use, a future diagnosis of opioid use disorder, pain-related ED visits, and future opioid-related admissions. Persistent opioid use was identified as having filled at least 120 days' supply or 10 or more

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Table 1. Summary of the OSI components[a]

OSI component	Description
Prescribing dashboards	Aggregates facility-, provider-, and patient-level opioid prescription data to enable monitoring across key parameters, eg, high-dose prescribing, concomitant benzodiazepine prescribing, long-term opioid use. Leaders at each facility received reports and provided feedback to prescribers.
VA-DoD Clinical Practice Guideline	Provides clinical decision-making support and evidence-based clinical tools to guide safe opioid prescribing
Provider education	Directs educational outreach on opioid prescribing tailored to an individual provider's knowledge base via the VA Pharmacy Benefits Management Academic Detailing Services
Complementary and Integrative Health Initiative	Expands access to nonpharmacological interventions for pain including complementary and integrative health modalities, eg, acupuncture, biofeedback
Stepped Care Model and Pain Management Teams	Coordinates facility-level pain management teams to oversee care of patients with complex pain-prescribing needs, monitor key high-risk prescribing parameters, and provide feedback to clinicians

[a]DoD = Department of Defense; OSI = Opioid Safety Initiative; VA = Veterans Administration.

opioid prescriptions between 1 and 2 years after the start of treatment, as used in prior studies (19-21). Future diagnoses of opioid use disorder, pain-related ED visits, and opioid-related admissions were obtained using International Classification of Disease 9/10 codes (Supplementary Table 1, available online) (19).

Statistical Analysis

Baseline patient, treatment, and cancer characteristics were summarized as averages for continuous variables and percentages for categorical variables among patients in the pre- and post-OSI cohorts. Categorical and continuous variables were compared using χ^2 and Mann-Whitney *U* tests, respectively. An interrupted time series regression was used to evaluate changes in prescribing before and after the OSI (24). A slope change model with Poisson regression was used based on data distribution and the hypothesized intervention impact (ie, intervention's impact would occur more gradually over time as it was implemented). Models were evaluated for overdispersion and autocorrelation using residual plots and the partial autocorrelation function (24). For the primary endpoint of any new opioid prescription, there was a slope increase in the 12 months before the OSI's implementation. An additional regression segment was added to account for the slope change during this period. Model covariates were considered statistically significant with a 2-sided *P* value less than .05. Statistical analyses were performed using R version 3.5.3 (25). Future diagnoses of opioid use disorder and opioid-related admissions were assessed using cumulative time-to-event analysis for the first 3 years after cancer diagnosis, which allowed for a longer period of evaluation of these potentially delayed endpoints. Kaplan-Meier curves and the log-rank test were used to compare the pre-OSI and post-OSI cohorts.

In an exploratory analysis, we analyzed variation in the primary endpoint of new opioid prescriptions between VA facilities. This analysis included only facilities treating 100 or more patients over the study period. A time series analysis was performed at the facility level with generalized linear mixed effects models (unstructured variance-covariance structure) to account for variations in prescribing patterns at baseline and in response to the OSI. We compared mixed effects models using fixed estimates alone, a random intercept (facility level), and a random intercept plus random slope (facility level and OSI change) using Akaike information criterion, log likelihood, and a χ^2 test.

All statistical tests were 2-sided, and a *P* value less than .05 was considered statistically significant.

Results

The cohort included 42 064 opioid-naïve patients treated for cancer at the VHA. Most patients were male (95.4%) and had a diagnosis of prostate cancer (56.2%) (Table 2). There were differences in sex, primary cancer type, stage, and treatment between the pre-OSI and post-OSI groups that were small in magnitude but statistically significant. For the pre-OSI and post-OSI cohorts, definitive local therapy included surgery (51.4% and 50.1%, respectively), radiation therapy (45.1% and 46.5%), or both surgery and radiation (3.5% and 3.3%). A minority of patients (12.5% and 11.9%) were treated with cytotoxic chemotherapy.

Table 2. Baseline OSI eras

Risk factors	Pre-OSI (n = 19 382)	Post-OSI (n = 22 682)	P[a]
Mean age (SD), y	66.93 (8.07)	66.00 (8.21)	—
Sex			
Female	979 (5.0)	968 (4.3)	<.001
Male	18 408 (95.0)	21717 (95.7)	
CCI			
0	5802 (29.9)	6656 (29.4)	.16
1	3570 (18.4)	4086 (18.0)	
2	4325 (22.3)	5237 (23.1)	
3+	5680 (29.3)	6698 (29.5)	
Primary cancer			
Prostate	10 504 (54.2)	13 158 (58.0)	<.001
Breast	816 (4.2)	851 (3.8)	
Colon	2724 (14.1)	3201 (14.1)	
Lung	5338 (27.5)	5472 (24.1)	
Stage (AJCC 7th edition)			
I	5712 (29.5)	6250 (27.6)	<.001
II	9512 (49.1)	11 803 (52.0)	
III	3809 (19.7)	4285 (18.9)	
IV	349 (1.8)	344 (1.5)	
Local treatment			
Surgery	9961 (51.4)	11 375 (50.1)	.008
RT	8735 (45.1)	10 556 (46.5)	
Surgery + RT	686 (3.5)	751 (3.3)	
Chemotherapy	2426 (12.5)	2688 (11.9)	.04

[a]Categorical and continuous variables were compared using 2-sided χ^2 and Mann-Whitney *U* tests, respectively. AJCC = American Joint Committee on Cancer; CCI = Charlson Comorbidity Index; OSI = Opioid Safety Initiative; RT = = radiation therapy.

The incidence of new opioid prescriptions among cancer patients increased from 26.7% (95% confidence interval [CI] = 25.0% to 28.4%) in the first quarter (Q1) of 2011 to 50.6% (95% CI = 48.3% to 53.0%) in Q3 2013 before OSI implementation (Figure 1, A). On segmented regression, opioid prescriptions increased at a rate of 1.5% (95% CI = 1.2% to 1.8%) month-over-month from Q1 2011 to Q3 2012 and accelerated to a rate of increase of 3.3% (95% CI = 1.3% to 4.2%) month-over-month from Q4 2012 until Q3 2013. Following OSI implementation, the relative monthly rate of change for new opioid prescriptions decreased (−3.4%, 95% CI = −3.9% to −2.9%, *P* < .001), resulting in a net decrease of −0.3% (95% CI = −0.4% to −0.1%) per month (Figures 1, A and 2).

This analysis included patients treated across 119 VA facilities, with 96 treating over 100 patients during the study period. The median rate of new opioid prescriptions at the start of the study (2011) was 24.1% (interquartile range = 18.7%-36.6%) (Figure 3). In the post-OSI era, the median change in prescription rates between 2016 and 2014 decreased 3.5% (interquartile range = −12.6%-6.0%). Using Poisson regression, there was high degree of facility level variance for baseline prescribing rates (SD of linear predictor = 0.27) with less variance in the per-quarter response to the OSI (SD = 0.032) (Supplementary Table 2, available online). Introducing random effects for the model did statistically significantly improve model performance by Akaike information criterion and log likelihood test, indicating that there was variability in prescribing at the facility level. However, fixed effects estimates were not meaningfully different between models.

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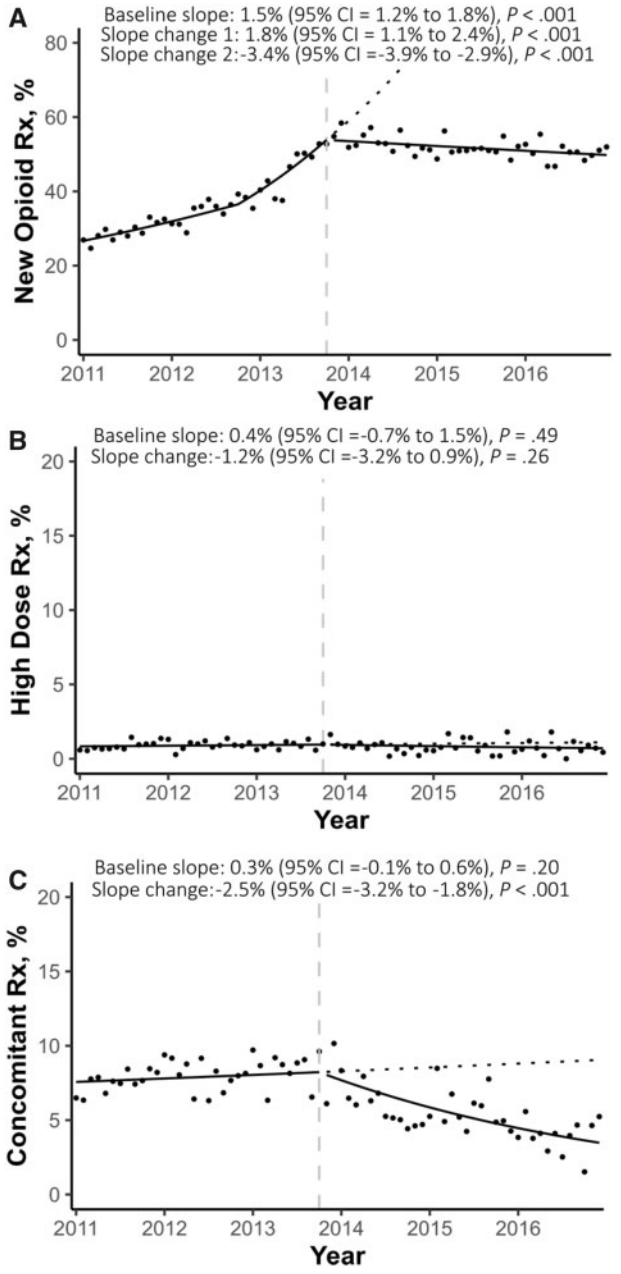

Figure 1. Opioid prescribing patterns over time. Prescribing patterns over time are shown for (**A**) any opioid prescription, (**B**) high-dose (≥100 morphine milligram equivalent) opioid prescription, and (**C**) concomitant opioid and benzodiazepine prescriptions. The percent change in slope per month is given with the 95% confidence interval (CI) and *P* value. Two-sided *P* values are derived from a Poisson regression model. The **solid lines** represent fit from segmented regression. The **dotted line** represents counterfactual without intervention. The **vertical dashed line** indicates the time of intervention. Rx = prescription.

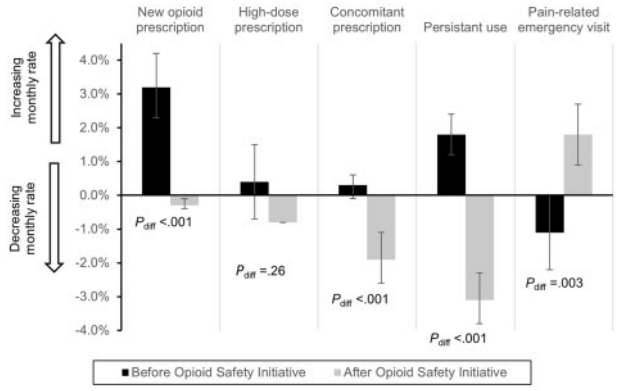

Figure 2. Rates of change in primary and secondary endpoints before and after the Opioid Safety Initiative. The bar graph indicates monthly rate of change on segmented regression for any opioid prescription, high-dose opioid prescription, concomitant opioid and benzodiazepine prescriptions, persistent opioid use, and pain-related emergency department visits. Two-sided *P* values are derived from a Poisson regression model.

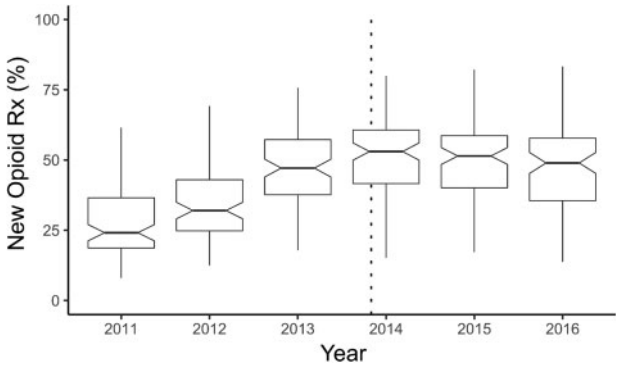

Figure 3. Box plot showing the rates of new opioid prescriptions by facility per year. The median (**horizontal line**), standard error of the mean (**wedge**), interquartile range (**box**), and upper and lower limits (**whiskers**) are shown. The **dashed black line** represents the mean prescription rate per quarter across facilities. Rx = prescription.

The incidence of high-dose opioid prescriptions among cancer patients was low and remained stable at 0.6% (95% CI = 0.3% to 0.9%), 0.9% (95% CI = 0.5% to 1.4%), and 0.7% (95% CI = 0.1% to 1.2%) for Q1 2011, Q3 2013, and Q4 2016, respectively (Figure 1, B). On segmented regression, there was no statistically significant difference in the monthly rate of change of high-dose opioid prescriptions before (0.4%, 95% CI = −0.7% to 1.5%, P = .49) or after (−0.8%, 95% CI = −2.2% to 1.3%, P = .26) OSI implementation (Figures 1 and 2). Pre-OSI, the incidence of concomitant benzodiazepine and opioid prescriptions among new cancer patients was 6.9% (95% CI = 5.9% to 7.9%) in Q1 2011 and 8.2 (95% CI = 6.9% to 9.5%) in Q3 2013. Three years after the OSI, the incidence was 3.5% (95% CI = 2.3% to 4.8%) in Q4 2016. There was no statistically significant month-over-month change in the incidence of concomitant prescriptions before the OSI (0.3%, 95% CI = −0.1% to 0.6%, P = .20) (Figure 1, C). After OSI implementation, incidence of concomitant prescriptions decreased with a relative rate of −1.9% (95% CI = −2.6% to −1.1%, P < .001) per month (Figure 2).

The incidence of persistent opioid use after treatment increased from 3.1% (95% CI = 2.4% to 3.8%) in Q1 2011 to 6.4% (95% CI = 5.2% to 7.5%) in Q3 2013 before the OSI and subsequently decreased to 2.0% (95% CI = 1.1% to 3.0%) in Q4 2016 (Figure 4, B). On segmented regression, there was a statistically significant increase in the incidence of persistent opioid use month-over-month prior the OSI (1.8%, 95% CI = 1.2% to 2.4%, P < .001) (Figure 4, A). Post-OSI, the monthly rate of change of persistent opioid use decreased (−5.7%, 95% CI = −6.8% to −4.7%, P < .001), with a net decrease of −3.1% (95% CI = −3.8% to

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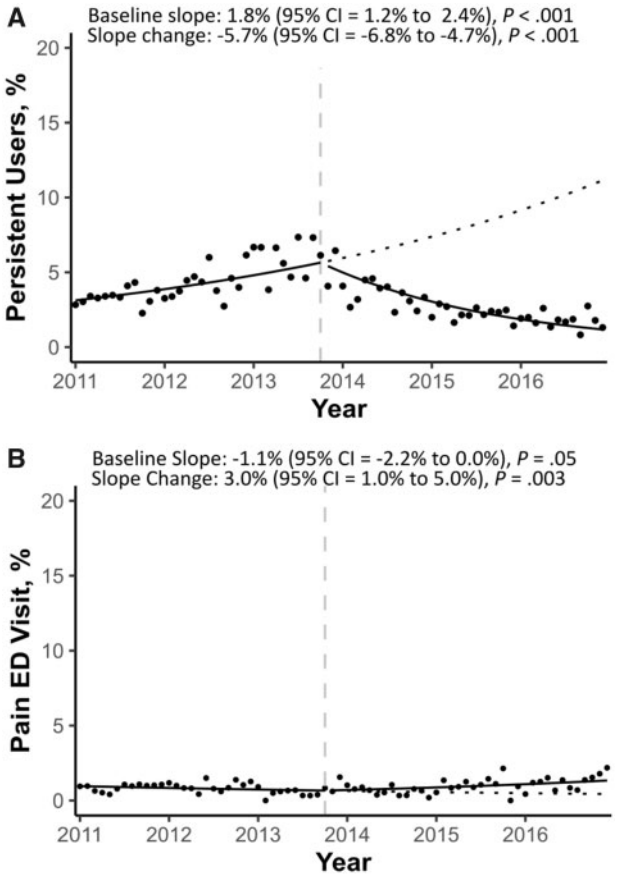

Figure 4. Longer-term opioid and opioid outcomes over time, including (**A**) persistent use at 2 years and (**B**) pain-related emergency department (ED) visits. The percent change in value per month is given with the 95% confidence interval (CI) and *P* value. Two-sided *P* values are derived from a Poisson regression model. The **solid lines** represent fit from segmented regression. The **dotted line** represents counterfactual without intervention. The **vertical dashed line** indicates the time of intervention.

−2.3%, $P < .001$) per month. Pain-related ED visits were generally stable in the pre-OSI period, with an incidence of 0.8% (95% CI = 0.4% to 1.0%) in Q1 2011 and 0.3% (95% CI = 0.1% to 0.6%) in Q3 2013. In the post-OSI period, the incidence of pain-related ED visits increased to 1.8% (95% CI = 0.9% to 2.7%) in Q4 2016, with a statistically significant increase in the monthly rate of change (+3.0%, 95% CI = 1.0% to 5.0%, $P = .003$) (Figures 2 and 4).

At 3 years, the cumulative incidence of opioid use disorder was 1.2% for both the pre-OSI and post-OSI cohorts (1.2% [95% CI = 1.0% to 1.3%] vs 1.2% [95% CI = 1.1% to 1.4%], $P = .77$) (Figure 5, A). The pre-OSI cohort experienced a higher 3-year cumulative incidence of opioid related admissions compared with the post-OSI cohort (0.9% [95% CI = 0.7% to 1.0%] vs 0.5% [95% CI = 0.4% to 0.6%], $P < .001$) (Figure 5, B).

Discussion

In this observational series, the incidence of opioid-naïve veterans receiving an opioid prescription during cancer treatment nearly doubled from 2011 until the implementation of the OSI in 2013. Although the cause of this increase is not clear, it does reflect national prescribing trends over the period (26). Within the VA there was no known system-wide approach to improve pain control and no reduction in availability of alternate pain control resources. The start of the OSI was associated with a statistically significant decrease in the incidence of new opioid prescriptions over time. High-dose opioid prescribing occurred in fewer than 2% of cancer patients and did not change statistically significantly over the course of this study. Concomitant benzodiazepine and opioid prescriptions were stable before the OSI and statistically significantly decreased after its deployment. Persistent opioid use after cancer treatment increased pre-OSI and then statistically significantly decreased over time after OSI implementation. Interestingly, there was a slight increase in the monthly incidence of pain-related ED visits, a potential indicator of inadequate pain control, after the OSI was implemented (27). Future diagnoses of opioid use disorder and opioid-related admissions were overall rare in this cohort. Importantly, however, the post-OSI cohort experienced a lower incidence of opioid-related admissions compared with the pre-OSI cohort.

Prior studies have demonstrated a decrease in opioid prescribing in response to federal, state, and institutional initiatives among noncancer populations (2,4,12,28,29). The impact of opioid risk reduction programs among patients with cancer is less studied. Graetz and colleagues (30) found that there was a slight decrease in the percentage of cancer patients receiving an opioid prescription after states implemented a mandatory prescription drug monitoring program. Opioid prescribing by oncologists for Medicare beneficiaries decreased from 2013 to 2017, which was attributed to opioid risk mitigation advocacy and policy (31).

This study expands on prior work by evaluating the impact of an opioid initiative in the United States' largest integrated health-care system and analyzing both acute and long-term prescribing trends. Importantly, concomitant benzodiazepine and opioid use as well as persistent use among survivors were found to decrease after implementing the OSI. Both of these prescribing patterns have been previously identified as high risk and are associated with adverse outcomes, including overdose and death (32-35). A prior study evaluating the impact of the OSI among all veterans similarly saw a decrease in overall opioid and concurrent benzodiazepine prescriptions (12). In contrast to that study, this cohort of cancer patients did not have declining rates of opioid prescriptions before the OSI. Furthermore, our cohort did not have a decline in high-dose prescriptions as was observed in the general cohort (12).

To our knowledge, this is the first study that has investigated the relationship between an opioid risk reduction program and downstream patient-centered outcomes, such as admissions in patients with cancer. Notably, the OSI was associated with decreases in new and high-risk opioid prescriptions, persistent opioid use, and opioid-related admissions. The slight increase in pain-related ED visits after the OSI may indicate higher rates of inadequate pain control for some patients.

Optimal pain management requires careful consideration of risks and benefits associated with treatments including opioid analgesics (36). Therefore, without more granular data on patient-level pain control or quality of life, it is challenging to comment on ideal opioid prescription patterns or rates for this cohort (37). Moreover, there is ongoing debate among providers and researchers as to what degree adverse opioid outcomes are a concern for cancer patients (6,37). Salz and colleagues (38) found that after 6 years from diagnosis, elderly cancer patients were not at increased risk for chronic opioid use compared with noncancer controls. A registry study of death certificate data showed that while there was a slight increase in the rate of opioid-related deaths among cancer patients during the opioid epidemic, the absolute incidence and growth rate were

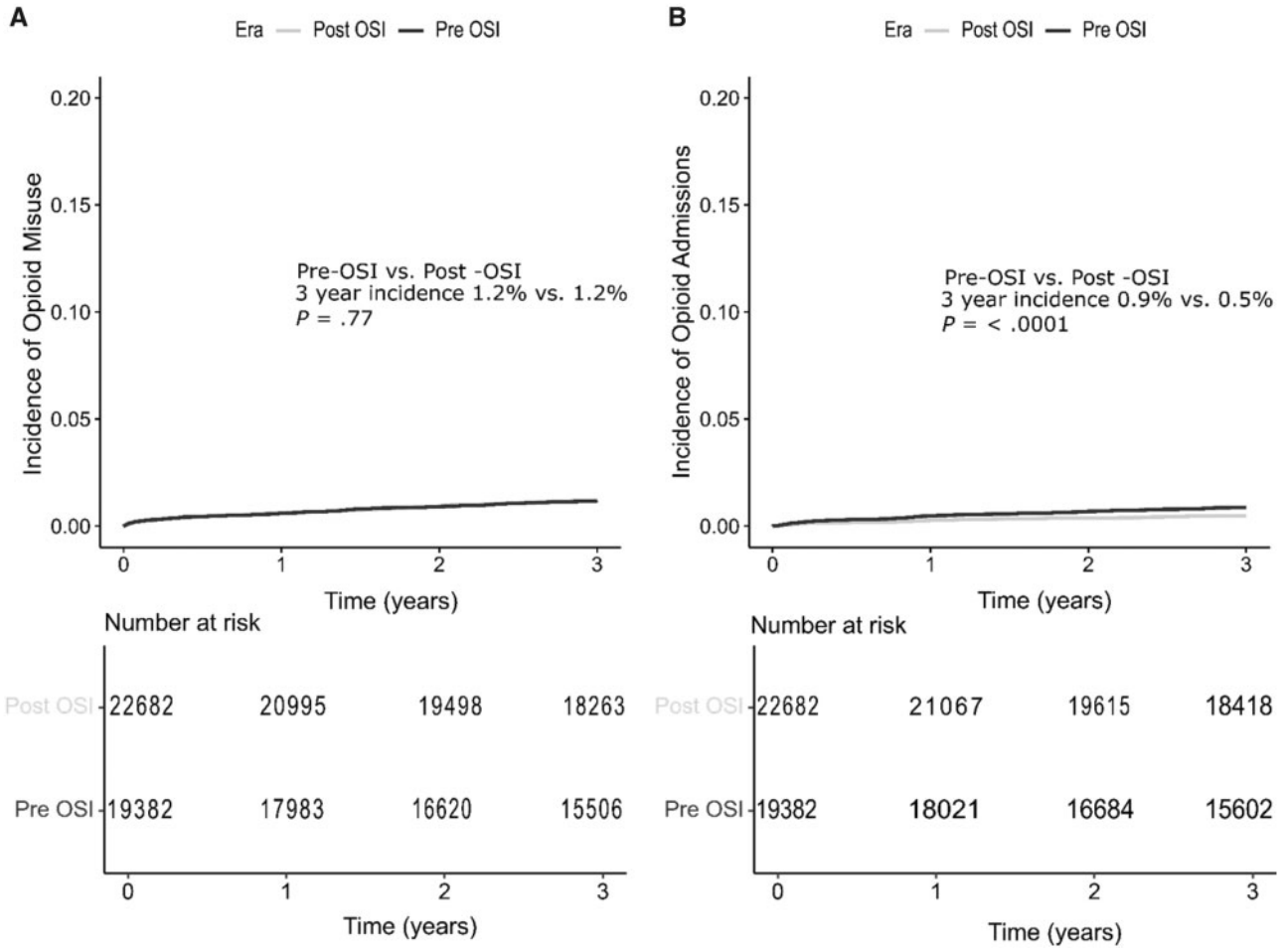

Figure 5. Cumulative incidence of (**A**) diagnosis of opioid misuse or dependence and (**B**) opioid-related admissions over time (years). Note: The gray and black curves are nearly overlaid in panel A because the cumulative incidence was highly similar between the 2 groups. Log-rank test was used to calculate 2-sided *P* values. OSI = opioid safety initiative.

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drastically lower than the general population (39). Despite this, however, a study by Jairam and colleagues (40) found that the incidence of ED visits related to opioid overdose doubled among cancer patients from 2006 to 2015. There is evidence that opioid use has decreased among cancer patients near the end of life when their need for analgesics could be the highest and the risk for future adverse events is likely the lowest (41). A recent analysis of Medicare part D data found that the percentage of patients with poor prognosis cancers within 30 days of death or hospice enrollment receiving an opioid prescription decreased from 2007 to 2017 while the incidence of pain-related ED visits increased (41). In this VHA cohort of nonmetastatic patients receiving definitive treatment, the incidences of opioid use disorder and opioid-related admissions were relatively rare. The rate of opioid related admissions, however, was slightly lower in the post-OSI cohort.

This study has potential limitations. The VHA pharmacy registry does not capture external prescriptions. It is possible that some patients sought alternate sources for medication outside of the VHA in response to more stringent opioid policies. It should also be noted that heterogeneity existed between the 114 facilities in the deployment of the OSI and how leaders responded to the OSI's dashboard reports. Our analysis suggests there was a high degree of baseline variation in prescribing rates between facilities and some variation in the response to the OSI. A more granular analysis of prescribing patterns at the provider level would be of academic and clinical interest but is, unfortunately, not feasible in this dataset.

It is also difficult to determine how much of the change in opioid prescribing patterns over this period can be attributed solely to the OSI. Other policies and cultural changes occurred both internally and externally that could affect opioid-prescribing patterns. Most notably, the VHA required providers to query state prescription drug-monitoring programs and integrated a clinical overdose risk score in February 2013 and June 2015, respectively (3). Despite variations in the OSI implementation across facilities and other policy changes over the study interval, a clear inflection point in opioid-prescribing rates is present at the OSI nationwide rollout date of October 2013, suggesting the initiative had an impact on prescribing patterns. Finally, it is not clear how the initiative at this integrated health system comprising mostly male patients translates into other health-care settings. Studying the impact of policy change in an integrated health-care system has advantages, though additional research will need to determine how opioid-related policy changes influence behavior in different health-care environments.

In conclusion, we found that the OSI was associated with a decrease in the rate of change in new opioid prescriptions, high-risk concurrent benzodiazepines prescriptions, and persistent opioid use. Opioid-related admissions were rare for all patients but statistically significantly lower in the post-OSI cohort. There was an increase in the rate of pain-related ED visits over time after implementing the OSI. The initiative was not associated with statistically significant changes in high-dose opioid prescribing or the future diagnosis of opioid addiction; however, these were rare at the outset of the study. Further research is needed to determine how policy initiatives can optimally guide opioid prescribing in cancer patients and, in particular, how opioid prescribing patterns affect pain control, quality of life, and function.

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Author contributions: LKV, VN and JDM were involved the conceptualization, data curation, project administration, methodology, formal analysis, writing—original draft and writing—review and editing. PR and MM were involved in formal analysis, methodology, writing—original draft and writing—review and editing. TF, LAL and RT were involved in writing—original draft and writing—review and editing.

Disclaimers: The contents do not represent the views of the US Department of Veterans Affairs or the US government. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

Patient level data are regulated by the Veterans Health Administration. Deidentified data summaries are available by request to the corresponding author (LKV).

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