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Outcome implications of benzodiazepine and opioid co-prescription in kidney transplant recipients

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Abstract

The outcomes of benzodiazepine and opioid co-prescription are not well-defined in transplant populations. We examined linked national transplant registry and pharmaceutical records to characterize benzodiazepine and opioid use in the years before and after transplant in large US cohort of kidney transplant recipients (2007-2016; N = 98 620), and associations (adjusted hazard ratio, $_{LCL}$aHR$_{UCL}$) with death and graft failure. Among the cohort, 15.6% filled benzodiazepine prescriptions in the year before transplant, and 14.0% filled benzodiazepine prescriptions in the year after transplant (short-acting, 9.5%; long-acting, 3.3%; both 1.1%). Use of short-acting benzodiazepines in the year before transplant was associated with a 22% increased risk of death in the year after transplant (aHR, $_{1.08}1.22_{1.38}$), while use of all classes in the year after transplant was associated with increased risk of death from >1 to 5 years (aHR: short-acting $_{1.29}1.39_{1.48}$; long-acting $_{1.12}1.25_{1.40}$; both $_{1.46}1.74_{2.07}$). Recipients who used benzodiazepines were also more likely to fill opioid prescriptions. Recipients who filled both classes of benzodiazepine and the highest level of opioids had a 2.9-fold increased risk of death compared to recipients who did not use either. Co-prescription of benzodiazepines and opioids in kidney transplant recipients is associated with increased mortality. Ongoing research is needed to understand mechanisms of risk relationships.

KEYWORDS
benzodiazepines, kidney transplantation, opioids, registries, risk factors

1 | INTRODUCTION

In the general population, prescription opioid use for the treatment of acute and chronic pain is associated with opioid-related complications, such as addiction, overdose, and death.[1-3] Use of benzodiazepines in combination with opioids may further increase these risks due to their additive depressant effects on the central nervous system. In a retrospective study using Medicare Part D claims data, concurrent use of benzodiazepines was associated with a 5-fold increased risk of opioid-related overdoses compared with opioid use alone.[4] Due to these risks, the 2016 Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain recommended that physicians avoid co-prescribing benzodiazepines and opioids whenever possible.[5] This recommendation also applies when managing pain in patients with chronic kidney disease.[6]

Previously, we have examined linkages of national transplant registries with pharmaceutical fill records to study opioid use in organ transplant recipients.[7-9] Administrative databases allow for nonintrusive identification of prescription fills to study prevalence and outcomes associated with medication use. Applying this methodology, we found that prescription opioid use in the year prior to kidney transplant was associated with an increased risk of arrhythmias, mental status changes, drug and alcohol abuse, and accidents in the first 3 years following transplant.[7] Pre- and post-transplant opioid use was associated with a graded increased risk of death and all-cause graft failure after kidney transplantation.[8,10] Similar risk relationships were recently documented among liver and heart transplant recipients.[9,11] Opioid use before living donor nephrectomy was also associated with increased risk of readmission after donation surgery.[12]

A systematic review of 15 relevant studies found prevalence of benzodiazepine and opioid use in dialysis patients of up to 26% and 36%, respectively, yet none of the included studies rigorously examined adverse clinical events.[13] In the kidney transplant population, concurrent use of benzodiazepines and opioids with outcomes has not been characterized. In this study, we examined linked registry and pharmacy fill records for a large national sample of kidney transplant recipients to study associations of pre- and post-transplant benzodiazepine and opioid use with death and graft loss after transplantation.

2 | METHODS

2.1 | Data sources

We conducted a retrospective cohort study using linked healthcare databases in the United States (US) to ascertain patient characteristics, pharmacy fill records, and outcome events for kidney transplant recipients. This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR system includes data on all donors, waitlist candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors.

Pharmacy claims data (PCD) were assembled by linking SRTR records for kidney transplant recipients with billing claims from Symphony Health Solutions, a large US pharmaceutical claims data warehouse that collects prescription drug fill records including self-paid fills and those reimbursed by private and public payers. The PCD comprise National Council for Prescription Drug Program format prescription claims aggregated from multiple sources including claims warehouses, retail pharmacies, and prescription benefit managers for approximately 60% of US retail pharmacy transactions. Individual claim records include the date of a given pharmacy fill with the national drug code identifying agent and dosage. After Institutional Review Board and HRSA approvals, PCD records were linked with SRTR records for kidney transplant recipients. We applied a deterministic deidentification strategy wherein patient identifiers (last name, first name, date of birth, sex, and ZIP code of residence) were transformed before delivery to the Saint Louis University researchers with Health Information Portability and Accountability Act and HITECH-certified encryption technology. The patient deidentification software employs multiple encryption algorithms in succession to guarantee that the resulting "token" containing encrypted patient identifiers can never be decrypted. However, the algorithm yields the same results for a given set of data elements, such that linkages by unique anonymous tokens are possible.

All direct identifiers were removed before the final dataset was available for analysis. Because of the large sample size, the anonymity of the patients studied, and the nonintrusive nature of the research, a waiver of informed consent was granted per the Department of Health and Human Services Code of Federal Regulations (Title 45, Part 46, Paragraph 46.116).

2.2 | Population and covariates

We considered all kidney transplant recipients who underwent transplant between 2007 and 2017 and who had 1 year of linked pre- and/or post-transplant pharmacy fill records. Transplant recipient clinical and demographic characteristics, as well as characteristics of the donated organ and other transplant factors, were defined by the OPTN Transplant Candidate Registration and Transplant Recipient Registration forms (Table 1).

Pharmacy fills for benzodiazepines and opioids in the year before and in the year after transplant were ascertained from the PCD records. We categorized benzodiazepine use as either short- or long-acting. Short-acting benzodiazepines included alprazolam, estazolam, lorazepam, midazolam, oxazepam, temazepam, and triazolam; long-acting benzodiazepines included chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, and flurazepam. Pharmacy fills for opioids in the year before and after transplant

TABLE 1 Distributions of clinical traits of kidney transplant recipients (n = 103 694) by class of benzodiazepine use in the year prior to transplant (2008-2017)

Baseline characteristics	No use (N = 87 533)	Short-acting (N = 10 456)	Long-acting (N = 4206)	Both (N = 1499)
Age, years		‡	‡	‡
<18	5.1	0.6	2.8	0.6
18 to 30	7.8	7.4	6.8	9.9
31 to 45	19.6	21.9	20.3	23.4
46 to 59	36.1	39.7	39.6	39.9
≥60	31.4	30.5	30.6	26.3
Female	38.1	48.0‡	44.1‡	47.5‡
Race		‡	‡	‡
White	49.2	62.2	63.3	69.1
African-American	28.2	20.2	20.1	15.1
Hispanic	15.0	13.8	11.9	12.9
Other	7.6	3.8	4.7	2.9
Highest level of education		‡	*	
College or higher	48.6	52.1	51.1	49.8
Grade/high school	45.4	43.5	42.9	45.0
Missing	6.0	4.4	6.0	5.1
Employment status		‡	‡	‡
Working	30.9	27.4	27.2	25.4
Not working	57.6	65.4	63.7	67.7
Missing	11.4	7.2	9.0	7.0
Health insurance type		‡	‡	*
Private	34.4	32.3	31.3	31.4
Public	65.5	67.6	68.7	68.6
Missing	0.1	0.1	0.0	0.1
Body mass index, kg/m^2		‡		*
<18.5	4.1	2.6	3.4	2.7
18.5-24.9	28.9	30.6	29.5	31.0
25.0-30.0	32.1	31.1	31.1	31.4
>30.0	33.7	34.4	34.7	33.9
Missing	1.3	1.4	1.3	1.0
Physical capacity status		†	†	‡
Not limited	48.6	48.6	48.4	52.4
Limited	5.0	5.9	6.3	6.5
Missing	46.4	45.5	45.3	41.1
Comorbid conditions				
Hypertension	73.2	73.6	72.2	73.1
Diabetes mellitus	32.5	32.1	30.5*	29.0*
Coronary artery disease	4.8	5.3*	6.1‡	6.4*
Cerebral vascular disease	2.1	2.4	2.7*	2.2
Peripheral vascular disease	6.8	7.2	7.9*	7.3
COPD	1.2	1.7 ‡	1.6*	1.3
Cause of ESRD		‡	‡	‡
Hypertension	25.1	23.4	22.0	20.5
Diabetes mellitus	24.5	23.6	23.2	21.0

(Continues)

TABLE 1 (Continued)

Baseline characteristics	No use (N = 87 533)	Short-acting (N = 10 456)	Long-acting (N = 4206)	Both (N = 1499)
Glomerulonephritis	23.1	25.1	24.1	27.9
Polycystic kidney disease	9.5	10.2	10.8	10.5
Other	17.8	17.8	19.9	20.1
Duration of dialysis, months		‡	‡	‡
None (pre-emptive)	18.1	12.7	13.6	9.1
0.1-24	28.3	31.2	29.1	33.8
25-60	29.8	32.0	33.2	33.7
>60	23.4	23.7	23.7	23.1
Missing	0.3	0.3	0.4	0.3
Peak PRA level, %		‡	‡	‡
<10	71.5	66.5	68.1	66.0
10 to 79	19.0	20.7	20.1	21.6
≥80	9.3	12.4	11.5	12.3
Missing	0.3	0.3	0.3	0.2
HLA mismatches		‡		†
Zero A, B, DR	6.8	7.9	7.4	9.5
Zero DR	11.4	11.9	11.3	11.9
Other	81.8	80.2	81.3	78.7
Previous organ transplant	13.7	17.8‡	17.7‡	19.9‡
Era of current transplant			*	*
2008-2011	35.1	34.3	37.5	37.0
2012-2014	36.7	36.9	34.9	37.8
2015-2017	28.1	28.8	27.7	25.2
Donor type		‡		
Living	34.4	37.2	35.0	36.7
Deceased (SCD)	45.4	44.6	45.8	44.5
Deceased (ECD)	9.1	7.9	8.5	8.3
Deceased (DCD)	11.1	10.4	10.8	10.5
Cold ischemia time, hours		*		
≤12	49.6	51.1	48.7	51.2
13-24	33.5	32.9	34.8	34.1
25-36	9.8	9.3	9.4	9.2
>36	2.4	2.0	2.0	1.9
Missing	4.8	4.8	5.2	3.7

Note: Data presented as column percentages (%).

Abbreviations: COPD, chronic obstructive pulmonary disease; DCD, donation after cardiac death; ECD, expanded criteria donor; ESRD, end-stage renal disease; HLA, human leukocyte antigens; PRA, panel reactive antibody; SCD, standard criteria donor.

*$P < .05$-.002.

†$P = .001$-.0002.

‡$P < .0001$.

were normalized to morphine equivalents (ME), according to conversion ratios (SDC, Table S1). Pre- and post-transplant ME were aggregated for each recipient and expressed as dose (mg) of annual ME exposure. We ranked annual ME exposure among recipients who filled opioid prescriptions by levels as follows: level I, 1-300 mg; level II, 301-600 mg; level III, 601-1000 mg; and level IV, >1000 mg per year, similar to previous methods.[7,9,10,12]

2.3 | Outcome measurements

The outcomes of interest were death and graft failure in the year after transplant for the pretransplant use analyses and in the >1 to 5 years after transplant for the posttransplant use analyses. Patient death was defined as death from any cause. In secondary analyses, we examined cause-specific death related to infections, malignancy, cardiovascular/

cerebrovascular, and other and unknown causes, as previously described.[14] All-cause graft failure included graft loss due to patient death, return to maintenance dialysis, or re-transplant. Patients were followed until the end of the study period (June 1, 2018).

2.4 | Statistical analyses

Datasets were merged and analyzed with SAS (Statistical Analysis Software) version 9.4 (SAS Institute Inc). Distributions of clinical and demographic characteristics among recipients with each class of pretransplant benzodiazepine use, compared with no benzodiazepine use, were compared by chi-square test. Propensity models for the likelihood of benzodiazepine use in the pretransplant period were constructed by multivariable logistic regression, and regression models were adjusted by stratification for quintile of propensity score, as per previous methods.[7-11,15] Adjusted associations of pretransplant benzodiazepine use with post-transplant death and all-cause graft failure (adjusted hazard ratio with 95% upper and lower confidence limits, $_{LCL}aHR_{UCL}$) were quantified by multivariate Cox regression including adjustment for recipient, donor, and transplant clinical factors. To assess impact of these medications on overall predictive capacity, we computed the change in c-statistics for models with and without the medications; for framing, we compared to the impact of clinical factors like comorbidities reported in the registry and body mass index (BMI). In all outcome analyses, we interpreted two-tailed $P < .05$ as statistically significant. The study followed guidelines for observational studies (SDC, Table S2).

3 | RESULTS

3.1 | Baseline characteristics of the kidney transplant recipients

Between 2008 and 2017, there were 165 039 US adult kidney transplant recipients in the SRTR database. Of these, 103 694 (62.8%) had available pretransplant medication data in the PCD and were generally similar to those without captured PCD fill data (SDC, Table S3). Overall, mean age at the time of transplant was 50.0 years (SD 15.6), 39.5% were female, and 51.4% were white (Table 1). In this cohort, 15.6% filled a prescription for a benzodiazepine in the year prior to transplant; 10.1% were prescribed a short-acting benzodiazepine, 4.1% a long-acting benzodiazepine, and 1.4% both. Patients who filled benzodiazepines were more likely to be aged 46-59 years, female, white, or unemployed, or to have a history of previous organ transplant, than recipients without a benzodiazepine prescription fill in the year prior to transplant. Patterns were similar for kidney transplant recipients with benzodiazepine prescription fills in the year after transplant, during which 14.0% of recipients filled benzodiazepines (short-acting 9.5%, long-acting 3.3%, and both 1.1%; SDC, Table S4).

3.2 | Death and graft failure according to pre- and post-transplant benzodiazepine use

Compared with those who did not use benzodiazepines, recipients who filled short-acting benzodiazepine in the year prior to transplant had a 22% increased risk of death in the first year after transplant (aHR, $_{1.08}1.22_{1.38}$) and a 14% lower risk of death-censored graft failure (aHR, $_{0.75}0.86_{0.99}$) (SDC, Table S5). There was no significant association of pretransplant use of long-acting benzodiazepines with death or graft failure over the first year post-transplant.

Risk relationships were more pronounced for benzodiazepine use in the first year post-transplant with death and graft failure in the subsequent >1 to 5 years (SDC, Table S6). For example, compared with no use, use of all classes of benzodiazepines was associated with increased risk of mortality over the next 4 years (aHR: short-acting $_{1.29}1.39_{1.48}$; long-acting $_{1.12}1.25_{1.40}$; both $_{1.46}1.74_{2.07}$). Use of both long- and short-acting benzodiazepines in the year after transplant was also associated with a 39% increased risk of all-cause graft failure (aHR, $_{1.21}1.39_{1.60}$) and a 14% increased risk of death-censored graft failure (aHR, $_{0.93}1.14_{1.39}$) in the subsequent >1 to 5 years, although the latter association did not reach statistical significance.

3.3 | Patterns of pre- and post-transplant benzodiazepine and opioid use

In the study cohort, 40.2% of recipients filled a prescription for an opioid in the year prior to transplant, while 27.4% filled a prescription in the year after transplant. In the years before and after transplant, recipients who filled a prescription for a benzodiazepine were also likely to fill an opioid prescription (Figure 1). The amount of opioid use (based on ME level) prescribed to recipients was similar in the short- and long-acting benzodiazepine groups. By comparison, patients who were prescribed both short- and long-acting benzodiazepines were more likely to be co-prescribed higher levels of opioids. Similarly, recipients who were prescribed both classes of benzodiazepines in the year prior to transplant were also more likely to be prescribed both classes in the year after transplant (Figure S1).

3.4 | Death and graft failure according to benzodiazepine and opioid use

After adjustment for demographic and clinical factors, high-level opioid use in the year prior to transplant was associated with increased risk of death in the first year post-transplant (SDC, Table S5). While significant interactions of benzodiazepines and opioids were not detected, there appeared to be additive mortality risks in patients who filled both benzodiazepine and opioids. Compared with opioid and benzodiazepine nonusers, the risk of death for recipients with high-level opioid use was 57% higher for those who did not use benzodiazepines and rose to over 2.5-fold for recipients who used both classes of benzodiazepines. Use of all classes of benzodiazepine use in the year

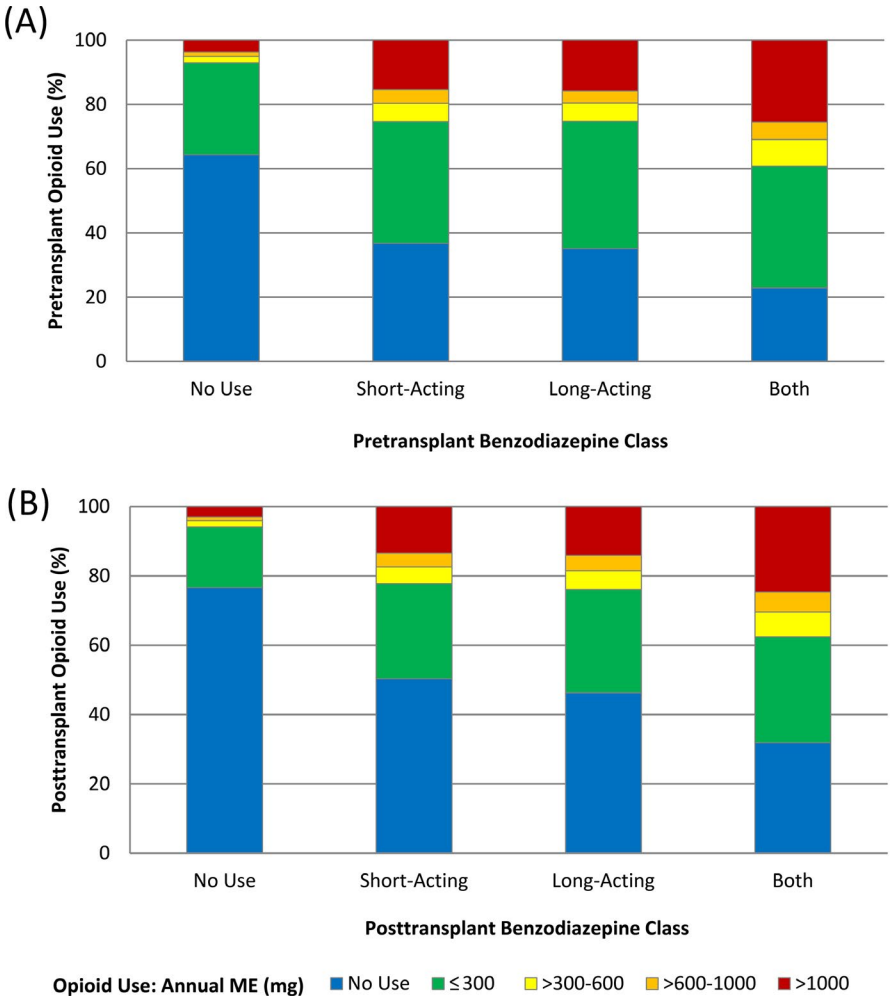

FIGURE 1 Pre- (A) and post-transplant (B) opioid use according to class of benzodiazepine use

following transplant was associated with graded increase in the risk of death and graft failure in the subsequent >1 to 5 years that rose with higher levels of opioid use in the period (Figure 2; SDC, Table S6). For example, recipients with the highest level of post-transplant opioid use who filled both classes of benzodiazepines had a 2.9-fold increased risk of death compared with recipients who did not fill either agent.

In addition to these associations, the risk of death and graft failure in the >1 to 5 years after transplant was significantly ($P < .05$) higher for recipients with a history of coronary artery disease, peripheral vascular disease, or chronic obstructive pulmonary disease, and for recipients with longer pretransplant dialysis duration (>60 months vs 0.1-24 months), those with a previous organ transplant, those who received extended criteria donor kidneys (vs standard criteria donor [SCD] kidneys), and those with longer cold ischemia time (vs <12 hours) (SDC, Table S6). The risk of death and graft failure in the >1 to 5 years after transplant was lower in Hispanic recipients (vs white), and in those who were employed, who received pre-emptive transplants (vs those who spent 0.1-24 months on dialysis prior to transplant), who underwent transplant in more recent eras (vs 2007 to 2010), or who received living donor kidneys (vs SCD). Associations were similar for death and graft failure in the first year post-transplant (SDC, Table S5).

The impact of benzodiazepines and opioids on overall predictive capacity quantified by c-statistics was similar to that of the group of comorbidities captured in the SRTR registry and greater than that of BMI (Table S7). Pretransplant benzodiazepine and opioid use contributed 1.5% to overall prediction of first year post-transplant death, compared to 2.6% impact of combined comorbidities and 0.3% impact of BMI. Post-transplant benzodiazepine and opioid use contributed 3.9% to overall prediction of >1 to 5 years post-transplant death, compared to 2.1% impact of combined comorbidities and 0.3% impact of BMI.

We examined cause of death reported to the registry. In the first year after transplant, distribution of reported causes of death included: infection, 20.4%; cardiovascular, 24.4%; malignancy, 4.9%; other, 31.5%; and unknown, 18.8%. Compared to recipients with no evidence of benzodiazepine or opioid use in the year prior to transplant, recipients with both classes of benzodiazepine and the highest level of opioid use had a 2-fold increased risk of death due to infection (aHR, ${}_{1.18}2.20_{4.12}$), other (aHR, ${}_{1.14}2.85_{2.99}$), and unknown causes (aHR, ${}_{1.52}2.08_{2.83}$), but no statistically significant increase risk of death due to cardiovascular causes (aHR, ${}_{0.74}1.48_{2.98}$) or malignancy (aHR, ${}_{0.40}1.07_{2.85}$) (SDC, Table S8). Similar results were found in the post-transplant use analyses (aHR, infection:

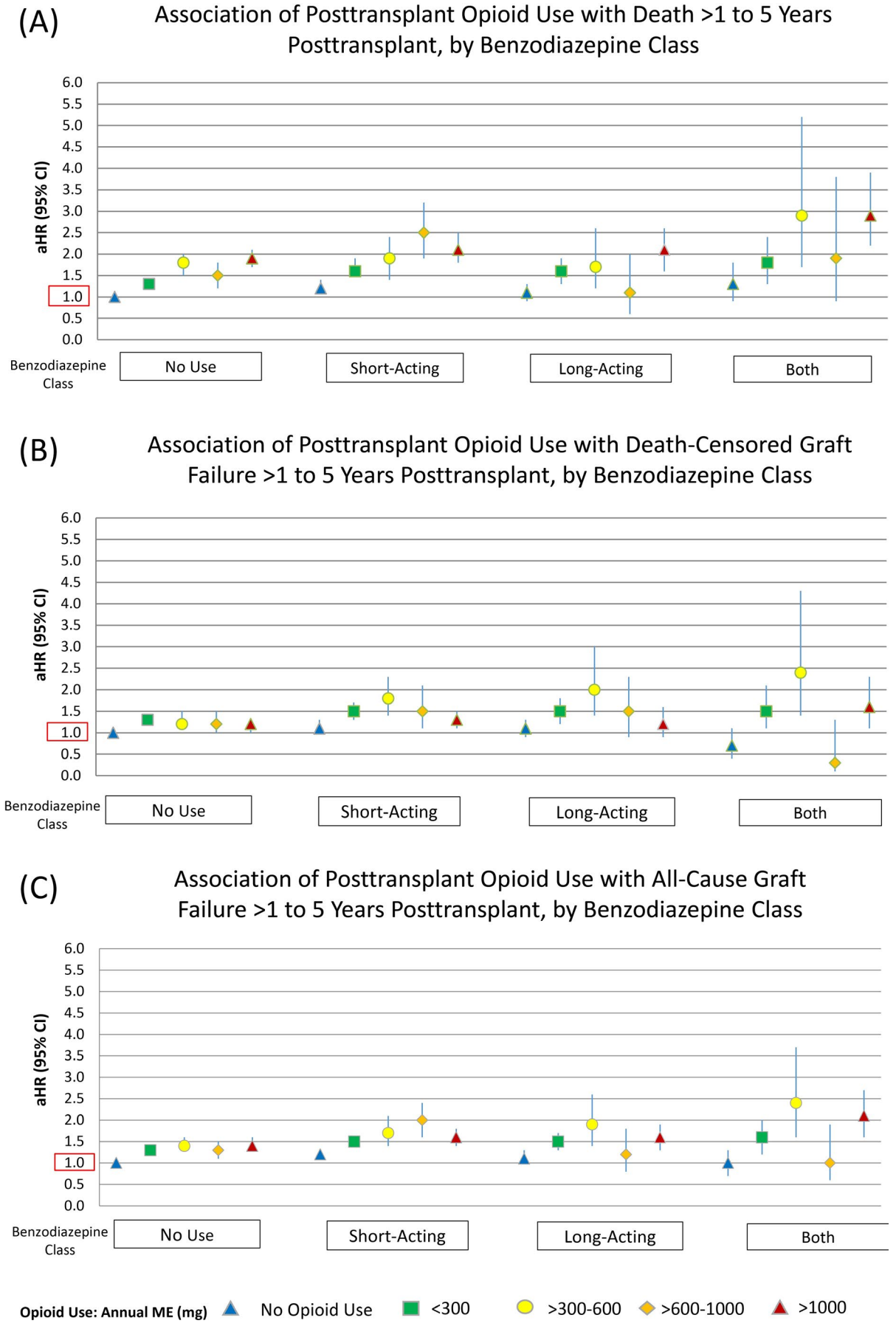

FIGURE 2 Adjusted associations of post-transplant benzodiazepine and opioid use and death and graft failure in the subsequent >1 to 5 y

$_{1.80}3.63_{7.32}$; cardiovascular: $_{0.51}1.37_{3.67}$; malignancy: $_{0.63}1.68_{4.49}$; other: $_{0.95}1.83_{3.53}$; unknown: $_{2.01}2.77_{3.81}$) (SDC, Table S9).

4 | DISCUSSION

We examined novel linkages of national transplant registry data with a pharmaceutical claims warehouse to retrospectively study benzodiazepine and opioid prescription fills among a large national cohort of US kidney transplant recipients. We found that use of both short- and long-acting benzodiazepines in the first year after transplant was associated with a 74% increased risk of death in the subsequent >1 to 5 years compared with no use. Transplant recipients who used benzodiazepines were also more likely to fill opioid prescriptions such that after transplant, opioid fills rose from 23.3% among benzodiazepine nonusers to 68.2% among those who filled both short- and long-acting benzodiazepines. Recipients with high-level post-transplant opioid use who used both classes of benzodiazepine had 2.9-fold increased risk of death compared with patients who did not use either medication, suggesting additive effects of these agents on post-transplant mortality risk.

Despite the burden of mood disorders and chronic pain in patients with end-stage kidney disease, use of benzodiazepines and opioids is understudied in this population. A systematic review of 15 studies found prevalence of benzodiazepine use in dialysis patients ranging from 8% to 26%, and prevalence of opioid use ranging from 5% to 36%.[13] The review highlights the problems of anxiety, depression, and pain in the dialysis population, and the variability of medication use and methods of drug reporting across centers. Kidney transplant recipients are typically a healthier segment of the population with kidney failure given the rigorous screening and selection process required in the assessment of transplant candidates. Our study found that 16% of kidney transplant recipients filled a prescription for a benzodiazepine in the year prior to transplant, and 40% filled a prescription for an opioid, similar to the prevalence reported in the systematic review. Often, unstable psychiatric illness is considered a contraindication to transplant due to concerns about medication nonadherence and poor outcomes. Thus, kidney transplant recipients with a history of benzodiazepine use may represent the subset of dialysis patients with well-controlled mood disorders. In contrast, chronic pain for patients on the waiting list is not uncommon and can be related to comorbidity (eg diabetes mellitus) or dialysis complications (eg calciphylaxis or steal syndrome with arteriovenous fistulas).[16-18] This may explain why pretransplant benzodiazepine use was relatively uncommon in our cohort while nearly half of recipients filled an opioid prescription in the year prior to surgery.

Concurrent use of benzodiazepines and opioids should be avoided in the general population and in patients with chronic kidney disease.[6,19] The adverse effects of benzodiazepines and opioids in dialysis patients are poorly characterized,[13] but there are concerns that the clinical consequences may be potentiated in this population due to reduced clearance of active metabolites. Our study is one of the first to report on patterns of pre- and post-transplant benzodiazepine and opioid use in kidney transplant recipients and associated outcomes. We found that recipients who filled a prescription for a benzodiazepine were more likely to fill a prescription for an opioid in the pre- and post-transplant periods. Recipients who were prescribed both short- and long-acting benzodiazepines were also more likely to be co-prescribed higher levels of opioids. Use of both classes of benzodiazepines in combination with high-level opioid use may be a marker of the burden of illness for dialysis patients on the waiting list, including the dual diagnosis of mood disorders and chronic pain, or may relate to multiple physician prescribers involved in the care of these complex patients.

In the general population, concurrent use of benzodiazepines and opioids leads to increased opioid-related overdoses due to the additive respiratory depressant effects.[4,20] In one study, prescription fills for both benzodiazepines and opioids were associated with a 2-fold higher risk of emergency room visits or hospitalizations for opioid-related overdoses, compared with prescription fills for opioids alone.[20] Almost 30% of fatal opioid-related overdoses in the US are thought to also involve benzodiazepines.[20] We found that recipients who filled both classes of benzodiazepines along with the highest level of opioids were at highest risk of death, especially if these prescriptions were filled within the first year after transplant. This suggests an additive effect on post-transplant risks for recipients with these co-prescriptions.

Our study is one of the largest to examine benzodiazepine and opioid use and the effects on post-transplant outcomes, such as death and graft loss. We used novel linkages of a transplant registry to electronic prescription fills as a nonobtrusive method to identify opioid use that circumvents biases related to self-report. This study also has limitations. While prescription fill records may be more accurate than patient self-reporting, we may have underestimated benzodiazepine and opioid use given that we were unable to account for illicit drug use or prescription fills at pharmacies not included in our databases. These patients would likely still be categorized as high-level users if they filled most of their benzodiazepine and opioid prescriptions at the same pharmacy as their immunosuppressive medications. As mentioned, we lacked details on cause of death and on biopsy results to ascertain cause of graft loss. Given the retrospective nature of the study design, we can only describe associations, not causation. Benzodiazepine and opioid use may reflect complex comorbidity or may be markers of riskier patient behaviors, such as nonadherence, that may lead to poorer outcomes.

The transplant evaluation process is an opportunity to perform a detailed medication review to identify clinical risk factors and mitigate any potential post-transplant drug interactions. Use of benzodiazepines and opioids appears to predict increased risk of death and graft loss after kidney transplantation. Ongoing research is needed to better understand the mechanisms of these risk relationships in this unique patient population.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflict of interests to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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