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Mortality Risk in Chronic Kidney Disease Patients Transitioning to Dialysis: Impact of Opiate and Non-Opiate Use

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Abstract

Background: Population-based studies show there is a high prevalence of chronic kidney disease (CKD) patients suffering from chronic pain. While opiates are frequently prescribed in non-dialysis dependent CKD (NDD-CKD) patients, there may be toxic accumulation of metabolites, particularly among those progressing to end-stage renal disease (ESRD). We examined the association of opiate vs. other analgesic use during the pre-ESRD period with post-ESRD mortality among NDD-CKD patients transitioning to dialysis.

Methods: We examined a national cohort of US Veterans with NDD-CKD who transitioned to dialysis over 2007–14. Among patients who received ≥1 prescription(s) in the Veterans Affairs (VA) Healthcare System within one year of transitioning to dialysis, we examined associations of pre-ESRD analgesic status, defined as opiate, gabapentin/pregabalin, other non-opiate analgesic, vs. no analgesic use, with post-ESRD mortality using multivariable Cox models.

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Authors' Contributions

ASY, KKZ, and CMR designed the study; ASY analyzed the data; ASY created the figures; ASY and CMR drafted and revised the paper; ASY, KKZ, ES, CP, JJS, ET, JTH, YO, PKP, ANA, DVN, CPK, and CMR provided critical revision of the manuscript; all authors approved the final version of the manuscript.

Disclosure Statement

None of the authors have relevant conflicts of interest to report.

Results: Among 57,764 patients who met eligibility criteria, pre-ESRD opiate and gabapentin/pregabalin use were each associated with higher post-ESRD mortality (ref: no analgesic use), whereas non-opiate analgesic use was not associated with higher mortality in expanded case-mix analyses: HRs (95%CIs) 1.07 (1.05–1.10), 1.07 (1.01–1.13), and 1.00 (0.94–1.06), respectively. In secondary analyses, increasing frequency of opiate prescriptions exceeding one opiate prescription in the one-year pre-ESRD period was associated with incrementally higher post-ESRD mortality (ref: no analgesic use).

Conclusions: In NDD-CKD patients transitioning to dialysis, pre-ESRD opiate and gabapentin/pregabalin use were associated with higher post-ESRD mortality, whereas non-opiate analgesic use was not associated with death. There was a graded association between increasing frequency of pre-ESRD opiate use and incrementally higher mortality.

Keywords

Opiate; analgesic; mortality; dialysis; transition

Introduction

In the United States (US), chronic pain is a highly prevalent condition estimated to affect over 20% of the population (i.e., 50 million US adults).[1] While multifactorial, chronic pain accounts for 20% of ambulatory visits[2] and $560 billion in annual direct medical (i.e., health care services) and indirect medical (i.e., lost productivity) costs.[3] Furthermore, analgesics account for 12% of all prescriptions in the general population.[4,5] For this reason, one of the national *Healthy People 2020* objectives has been to "decrease the prevalence of adults having high-impact chronic pain."[1,6]

Epidemiologic data show that chronic pain is disproportionately more common in chronic kidney disease (CKD) patients, including those receiving dialysis (i.e., affecting 50% to 60% of advanced non-dialysis dependent [NDD] CKD and end-stage renal disease patients, respectively[7–9]). Indeed, in the CKD population chronic pain has been associated with adverse sequelae, including impaired health-related quality of life, disability, kidney function decline, hospitalization, and higher death risk.[9–14] However, the treatment of chronic pain in this population is oftentimes suboptimal, owing to limited analgesic options due to altered pharmacokinetics and pharmacodynamics in CKD.[15]

Large population-based studies suggest that opiates are one of the most commonly prescribed analgesics in CKD patients.[16–18] Despite recent registry data showing the ill effects of opiates in the ESRD population,[16,17] as well as widespread recognition of the US "Opioid Epidemic" as a public health crisis,[19] clinicians may be more inclined to prescribe opiates than non-opiate analgesics in the NDD-CKD population due to concerns about the potential accumulation and/or toxicities of the latter,[20] including kidney injury/damage (i.e., non-steroidal anti-inflammatory drugs[21,22]), cardiac arrhythmias (i.e., tricyclic anti-depressants[23]), and neurotoxicity (i.e., gabapentin and pregabalin[24]). To date, there have been a paucity of studies examining the impact of opiate analgesic use upon outcomes specifically among advanced NDD-CKD patients transitioning to ESRD. Thus, to better inform clinical decision making, through linkage of pre-ESRD data from the national

Veterans Affairs (VA) database with post-ESRD registries (e.g., United States Renal Data System [USRDS]),[25] we sought to examine the relationship between pre-ESRD opiate vs. other analgesic use during the pre-dialysis transition period with post-ESRD mortality among US Veterans with incident ESRD.

Materials and Methods

Source Population

We conducted a cohort study with longitudinal data from the Transition of Care in CKD (TC-CKD) study,[25–29] a retrospective cohort study examining US Veterans transitioning to renal replacement therapy over the period of October 1, 2007 through September 30, 2014. Our source population consisted of 85,505 patients from the national VA database who transitioned to dialysis over the period of October 1st, 2007 to March 31, 2014. Patients were included if 1) were age 18 years or older at the time of study entry, 2) transitioned to dialysis, 3) had complete person-time follow up data (i.e., no missing death/censoring events data), and 4) had evidence of at least one or more prescriptions from the VA healthcare system within the five-year pre-ESRD period prior to transitioning to dialysis.

Patients were categorized into three analytic cohorts based on having pre-ESRD observation ("prelude") exposure intervals of one, two, or five years prior to transitioning to dialysis.[25] We *a priori* defined the one-year prelude period cohort as our primary cohort. The study was approved by the Institutional Review Boards of the University of California Irvine Medical Center, VA Long Beach Healthcare System, and Memphis VA Medical Center.

Exposure Ascertainment

Our exposure of interest was pre-ESRD opiate vs. other analgesic use (parsed as gabapentin/pregabalin, other non-opiate analgesic, vs. no analgesic use) over the one-year prelude period. As noted above, as some Veterans may largely receive prescriptions from non-VA medical centers, we required that all patients have evidence of one or more prescriptions from the VA healthcare system in order to reduce risk of exposure misclassification due to non-capture of non-VA prescriptions. Given that patients with vs. without analgesic use and chronic pain may be inherently different,[9] among patients who did not have pre-ESRD opiate use we separately examined those with gabapentin/pregabalin use vs. other non-opiate analgesic use vs. no analgesic use. In addition to gabapentin/pregabalin, other non-opiate analgesics examined included acetaminophen, non-steroidal anti-inflammatory drugs, aspirin, barbiturates, and local anesthetics.

In primary analyses, we categorized patients as those with opiate analgesic, gabapentin/pregabalin, other non-opiate analgesic, vs. no analgesic use ascertained from VA prescription data. In secondary analyses, we examined frequency of opiate prescriptions, categorized as >0–1, >1–2, >2–3, >3–4, and >4 prescriptions over the one-year prelude period. In sensitivity analyses, we examined the two-year and five-year prelude cohorts (Suppl. Fig. 1).

Outcome Ascertainment

Our primary outcome of interest was post-ESRD all-cause mortality risk. Follow-up began the day after dialysis initiation and ended at the time the patient experienced a censoring or death event. Patients were censored for kidney transplantation, loss to follow-up, or the last date of available follow-up data (September 2, 2014), whichever occurred first. All-cause mortality data, censoring events, and associated dates were obtained from VA, Center for Medicare and Medicaid Services (CMS), and USRDS data sources.

Socio-demographic, Comorbidity, Medication, Laboratory, and Pain Score Data

Data from the USRDS Patient and Medical Evidence files were used to determine patients' baseline socio-demographic information (e.g., age, sex, race, ethnicity) at the time of dialysis initiation. Cause of ESRD was obtained from CMS data, and information on initial dialysis modality was obtained from USRDS sources. Information about comorbidities at the time of dialysis initiation were extracted from the VA Inpatient and Outpatient Medical SAS datasets[30] and CMS datasets using ICD-9 diagnostic and procedure codes and Current Procedural Terminology codes as well as from VA/CMS data.[9,31,32] Charlson Comorbidity Index (CCI) scores were estimated using the Deyo modification for administrative datasets without including kidney disease.[33] Body mass index data were obtained from the VA Vital Status file. Medication data were obtained from both CMS Part D and VA pharmacy dispensation records.[34] Laboratory data were obtained from the Decision Support System-National Data Extracts Laboratory Results files, and were defined as the average of each covariate during the one-year prelude period preceding dialysis initiation.[35] VA Corporate Data Warehouse-LabChem data files were used to extract data about pre-dialysis serum creatinine.[36] Using serum creatinine and demographic data, estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration equation.[37]

Information on patients' presence and severity of pain was ascertained using self-reported pain score data. In the VA healthcare setting, patients are routinely screened about their experience of pain, which is documented in medical record as part of a system-wide approach to improve pain management. Patients are queried about presence and intensity of pain and pain intensity using the 0-to-10 Numeric Rating Scale in which "0" equals no pain and "10" represents the worst possible pain.[38]

Statistical Analysis

We estimated the association between pre-ESRD opiate analgesic vs. gabapentin/pregabalin vs. non-opiate analgesic vs. no analgesic use status and post-ESRD mortality using Cox models with four levels of adjustment using the following covariates:

1. *Minimally adjusted model:* Patient's calendar quarter of dialysis initiation to account for secular changes in care over time;
2. *Case-mix model:* Minimally adjusted model covariates, plus age, sex, race, ethnicity, and diabetes;
3. *Expanded case-mix model:* Case-mix model covariates, plus cause of ESRD, initial dialysis modality, geographical region of residence, marital status,

congestive heart failure (CHF), coronary artery disease (CAD), cerebrovascular disease (CVD), depression, and Charlson Comorbidity Index (CCI) score;

4. *Expanded case-mix+laboratory model:* Expanded case-mix model covariates, plus serum albumin, eGFR averaged over the one-year prelude period (proxy of residual kidney function), and last eGFR level measured prior to dialysis initiation (proxy of dialysis practice patterns).

We *a priori* defined the expanded case-mix model as our preferred model, which included core socio-demographic measures and comorbidity confounders of the association between analgesic use status and mortality. There were no missing data for age, sex, race, ethnicity, cause of ESRD, comorbidities, and initial dialysis modality; remaining covariates had <1% missing values, except for geographical region of residence (1%), marital status (3%), serum albumin (38%), and eGFR (33%). Hence, further adjustment for potential confounders in expanded case-mix+laboratory models were conducted as secondary analyses. To account for pain severity and presence of neuropathy as confounders of the association between analgesic use status and mortality, we also conducted sensitivity analyses that incrementally adjusted for 1) pain score in expanded case-mix+laboratory+pain score models, and 2) presence vs. absence of neuropathy in expanded case-mix+laboratory+pain score +neuropathy models, respectively. To assess the impact of opiate duration of action and survival, we conducted sensitivity analyses in we separately examined patients with short-acting opiate use, long-acting opiate use, and both short-acting and long-acting opiate use. To gain insights into the impact of the settings of opiate use and outcomes, we also conducted sensitivity analyses in which we separately examined opiate use during hospitalization (i.e., which may serve as a proxy of opiate use around procedures) vs. opiate use in the ambulatory setting.

We conducted subgroup analyses of analgesic use status and all-cause mortality across clinically relevant subgroups. To address missing covariate data, we implemented multiple imputation using seven imputed datasets. Proportional hazards assumptions were confirmed by graphical analysis. Analogous analyses were conducted for secondary exposure definitions and sensitivity analyses. Analyses and figures were generated using SAS version 9.4 (SAS Institute Inc., Cary, NC), Stata version 13.1 (Stata Corporation, College Station, TX), and SigmaPlot Version 12.5 (Systat Software, San Jose, CA).

Results

Study Cohort

Among 57,764 patients who met eligibility criteria for the one-year prelude cohort, 50%, 4%, 4%, and 42% of patients had opiate, gabapentin/pregabalin, other non-opiate analgesic, and no analgesic use, respectively (Table 1 **and** Suppl. Fig. 1). Upon more granularly examining pre-ESRD opiate use, we found that 17%, 8%, 4%, 3%, and 18% of patients had >0–1, >1–2, >2–3, >3–4, and >4 prescriptions for opiate analgesics in the one-year prelude period, respectively (Suppl. Table 1).

Compared to patients without analgesic use, those with opiate analgesic use tended to be younger; were less likely to be White and more likely to be Black; were less likely to be

married and more likely to be divorced; were less likely to be living in the Northeast and more likely to be living in the South and West; were more likely to have diabetes, depression, and neuropathy and were less likely to have CAD and CVD; had higher pain scores; and had lower eGFR levels at dialysis initiation (Table 1). Compared to patients without analgesic use, those with non-opiate analgesic use (i.e., other than gabapentin/pregabalin) tended to be younger; were less likely to be White and more likely to be Black; were more likely to be single or divorced and less likely to be married; were less likely to live in the Northeast and Midwest and more likely to live in the South; were less likely to have CAD and CVD and more likely to have depression and neuropathy; and had lower eGFR levels at dialysis initiation. Notably, pain scores were similar among patients without analgesic use vs. those with non-opiate analgesic use.

Baseline characteristics stratified according to frequency of opiate analgesic use are shown in Supplementary Table 1. Compared to patients with less frequent use (i.e., >0–1 opiate prescription[s] in the one-year prelude period), those with more frequent use (i.e., >4 opiate prescriptions in the one-year prelude period) tended to be younger; were less likely to be married and more likely to be divorced; were less likely to live in the Northeast and more likely to live in the Midwest and South; were more likely to have in-center hemodialysis and less likely to have peritoneal dialysis as the initial dialysis modality; were more likely to have diabetes, CHF, CAD, depression, and neuropathy; had higher pain scores; and had higher eGFR levels averaged over the one-year prelude period and at the time of dialysis initiation.

Pre-ESRD Opiate, Gabapentin/Pregabalin, and Non-Opiate Analgesic Use and Post-ESRD Mortality

In primary analyses of the one-year prelude cohort, patients contributed a total of 114,722 patient-years of follow-up during which time 33,256 all-cause deaths occurred. Median (IQR) atrisk time was 19.1 (7.5, 36.4) months. In analyses adjusted for expanded case-mix covariates, compared with no pre-ESRD analgesic use, we found that pre-ESRD opiate use was associated with higher mortality risk in the one-year, two-year, and five-year prelude cohorts: adjusted HRs (aHRs) (95%CIs) 1.07 (1.05–1.10), 1.06 (1.04–1.09), and 1.07 (1.04–1.09), respectively (Fig. 1 **and** Suppl. Table 2). We also found that pre-ESRD gabapentin/pregabalin use was associated with higher mortality risk in the one-year, two-year, and five-year prelude cohorts in expanded case-mix adjusted analyses (ref: no pre-ESRD analgesic use): aHRs (95%CIs) 1.07 (1.01–1.13), 1.06 (1.00–1.12), and 1.07 (1.00–1.13), respectively. In contrast, other pre-ESRD non-opiate analgesic use was not associated with higher death risk in expanded case-mix models of the one-year, two-year, and five-year prelude cohorts (ref: no pre-ESRD analgesic use): aHRs 1.00 (0.941.06), 1.00 (0.94–1.06), and 1.04 (0.98–1.11), respectively. A similar pattern of findings was observed in analyses adjusted for expanded case-mix+laboratory covariates (Fig. 1 **and** Suppl. Table 2) and expanded case-mix+laboratory+pain score covariates (Suppl. Table 2).

Pre-ESRD Frequency of Opiate Use and Post-ESRD Mortality

In secondary analyses, we found that increasing frequency of pre-ESRD opiate prescription exceeding one opiate prescription[s] during the one-year prelude period was associated with

incrementally higher mortality risk in expanded case-mix models: aHRs (95% CI): 1.06 (1.02–1.11), 1.06 (1.01–1.12), 1.11 (1.04–1.19), and 1.22 (1.19–1.26) for >1–2, >2–3, >3–4, and >4 opiate prescriptions in the one-year prelude period, respectively (Fig. 2 **and** Suppl. Table 3). Pre-ESRD gabapentin/pregabalin use was also associated with higher mortality risk in the one-year prelude period in expanded case-mix analyses (ref: no pre-ESRD analgesic use): aHRs (95%CIs) 1.07 (1.02–1.13). In contrast, compared with no pre-ESRD analgesic use, pre-ESRD non-opiate analgesic use was not associated with higher death risk in expanded case-mix models: aHR (95% CI) 1.00 (0.94–1.07). Similar findings were observed following incremental adjustment for laboratory covariates (Fig. 2 **and** Suppl. Table 3), pain score (Suppl. Table 3), and neuropathy (Suppl. Table 4).

In expanded case-mix analyses of the two-year and five-year prelude cohorts, we also observed a graded association between increasing frequency of pre-ESRD opiate prescription exceeding one opiate prescription[s] during the corresponding prelude period and incrementally higher death risk, while pre-ESRD non-opiate analgesic prescription was not associated with higher mortality (Fig. 2 **and** Suppl. Table 3). A similar pattern of findings was observed in analyses incrementally adjusted for laboratory covariates (Fig. 2 **and** Suppl. Table 3) pain score (Suppl. Table 3), and neuropathy (Suppl. Table 4).

Pre-ESRD Opiate Analgesic Use and Post-ESRD Mortality Across Clinically Relevant Subgroups

In expanded case-mix analyses of the one-year prelude cohort, we observed effect modification on the basis on race, diabetes status, and CHF status (p-interaction=0.006, 0.02, and <0.001, respectively), such that opiate analgesic use had stronger associations with mortality in those who were White vs. Non-White; absence vs. presence of diabetes; and absence vs. presence of CHF (Fig. 3 **and** Suppl. Table 5). Similarly, gabapentin/pregabalin use had stronger associations with mortality in those who were White vs. those who were Non-White; absence vs. presence of diabetes; and absence vs. presence of CHF. However, we did not detect effect modification on the basis of age, ethnicity, initial dialysis modality, geographical region of residence, marital status, CCI score, CAD, CVD, depression, neuropathy, nor serum albumin: pinteraction=0.82, 0.70, 0.21, 0.30, 0.49, 0.06, 0.29, 0.31, 0.41, 0.63, and 0.15, respectively.

In expanded case-mix adjusted analyses, in all subgroups the nominal HRs for mortality for pre-ESRD opiate use were >1 except among patients who were Non-White or initial dialysis modality was home hemodialysis (ref: no pre-ESRD analgesic use). Nominal associations were statistically significant in the following subgroups: age <65 and ≥65 years; White; Non-Hispanic; diabetes present and absent; initial dialysis modality in-center hemodialysis and other; Midwest, South, and West geographic residence; single and married status; CCI score <5 and ≥5; CHF present and absent; CVD present and absent; CAD present and absent; depression present and absent; neuropathy present and absent; and serum albumin ≥3.5g/dL.

Pre-ESRD Opiate Analgesic Use and Post-ESRD Mortality Across Levels of Kidney Function

In secondary analyses, we observed a differential relationship between pre-ESRD analgesic use and post-ESRD mortality across strata of kidney function in the pre-ESRD period. In expanded case-mix analyses, pre-ESRD opiate analgesic use had stronger associations with mortality in those with eGFR ≥30 vs. <30ml/min/1.73m^2 (ref: no pre-ESRD analgesic use): aHRs (95%CIs) 1.20 (1.12–1.28) and 1.09 (1.05–1.12), respectively (p-interaction <0.001) (Suppl. Table 6). Conversely, pre-ESRD gabapentin/pregabalin and other non-opiate analgesic use was associated with higher death risk in patients with eGFR <30ml/min/1.73m^2 but not in those with eGFR ≥30ml/min/1.73m^2 (ref: no pre-ESRD analgesic use).

Opiate Duration of Action and Settings of Use

In sensitivity analyses, we examined whether there was a differential association between pre-ESRD opiate use and post-ESRD mortality according to opiate duration of action. In expanded case-mix analyses of the one-year prelude cohort, all types of opiate use were associated with higher mortality, with the strongest associations observed for patients who used both short-acting and long-acting opiates (ref: no pre-ESRD analgesic use): aHRs (95%CIs) 1.04 (1.01–1.07), 1.12 (1.06–1.18), 1.21 (1.16–1.26) for short-acting, long-acting, and both short-acting and long-acting opiate use, respectively (Suppl. Table 7).

We also examined whether there was a differential association between pre-ESRD opiate use and post-ESRD mortality according to the setting of use. In expanded case-mix analyses of the one-year prelude cohort, we found that pre-ESRD opiate use during hospitalization had an even stronger association with post-ESRD mortality than opiate use in the ambulatory setting (ref: no pre-ESRD analgesic use): aHRs (95%CIs) 1.20 (1.16–1.24) and 1.03 (1.01–1.06), respectively (Suppl. Table 8).

Discussion

In this large national cohort of US Veterans transitioning to ESRD, we observed that approximately half of all advanced CKD patients were prescribed opiate analgesics in the year prior to transitioning to dialysis. In analyses that accounted for differences in socio-demographic characteristics and comorbidity status, we found that patients with pre-ESRD opiate and gabapentin/pregabalin use each had higher post-ESRD death risk compared to those with no pre-ESRD analgesic use, whereas those with other pre-ESRD non-opiate analgesic use did not have higher mortality. Upon more granularly examining opiate utilization, we also found that patients with incrementally higher frequency of pre-ESRD opiate use had increasingly higher mortality risk. These findings were robust in multiple secondary and sensitivity analyses across different prelude cohorts and various levels of multivariable adjustment.

Several studies have documented a high prevalence of opiate use in the ESRD population and its adverse impact upon the health and survival of dialysis patients. In a systematic review of 15 studies across 12 countries over 1995 to 2006 by Wyne et al., the prevalence of opiate use ranged from 5% to 36% among dialysis patients; notably, prevalence of opiate use

positively correlated with increasing dialysis vintage.[18] In a seminal study of prevalent ESRD patients from the USRDS database with Medicare Part A, B, and D coverage over the period of 2006–2010 by Kimmel et al., over 60% of dialysis patients received at least one opiate prescription each year and over 20% received chronic opiate prescriptions annually.[17] In a subcohort of prevalent dialysis patients who received treatment in 2010, compared to those without an opiate prescription, patients with short-term (i.e., <90 days) or chronic opiate (i.e., ≥90 days) prescriptions had higher risk of mortality, hospitalization, and dialysis discontinuation. With respect to patient-centered outcomes, a cross-sectional analysis of baseline data from the Frequent Hemodialysis Network trial by Tamura et al. showed that opiate use was associated with cognitive impairment, namely impaired executive function.[39] In a subsequent study of patients receiving hemodialysis in 2011 from the USRDS database by Ishida et al., over 60% were prescribed opiates in that calendar year, and there was a dose-dependent association between opiate use and higher risk of altered mental status, falls, and fractures.[16]

To our knowledge, ours is the first study to examine the impact of pre-ESRD opiate use upon post-ESRD survival among advanced CKD patients transitioning to dialysis. Similar to the aforementioned studies, compared with patients who did not have pre-ESRD analgesic use, we found that pre-ESRD opiate analgesic use was associated with higher post-ESRD mortality. We also found that patients who used gabapentin/pregabalin without concomitant opiate use in the pre-ESRD prelude period also had higher post-ESRD death risk, corroborating other studies signaling the potential toxicities gabapentin/pregabalin use in dialysis patients (e.g., altered mental status, fall, fracture, death).[24,40,41] As patients with vs. without analgesic use may be inherently different with respect to chronic pain and health status, we also examined those with other non-opiate analgesic use (excluding gabapentin/pregabalin). In the overall cohort, patients with other pre-ESRD non-opiate analgesic use had similar survival compared to those with no analgesic use, even after accounting for differences in pain severity and specific pain conditions (i.e., neuropathy); however, in analyses stratified by kidney function, those who used other non-opiate analgesics with lower eGFRs (i.e., <30ml/min/1.73m^2) in the prelude period had higher post-ESRD death risk. While our data suggest they non-opiate analgesics other than gabapentin/pregabalin may be a preferred analgesic alternative to opiates in patients with mildto-moderate kidney dysfunction (eGFR ≥30ml/min/1.73m^2), there should be cautious administration and/or consideration of non-pharmacologic interventions in advanced CKD patients given alterations in drug absorption, bioavailability, distribution, metabolism, and excretion.[15]

Another noteworthy observation was the dose-dependent relationship between frequency of pre-ESRD opiate use and higher post-ESRD mortality risk. Consistent with the Kimmel et al.[17] and Ishida et al.[16] studies, our data signal the dangers of chronic opiate use and higher cumulative doses over time. It bears mention that more frequent opiate prescriptions were observed in patients with less social support (i.e., divorced) and those with underlying chronic disease, particularly depression. As mental health disorders oftentimes coexist with chronic pain and opiate use,[42] further research is needed to identify modifiable factors for opiate use as well as non-pharmacologic strategies to manage pain (i.e., psychotherapy) in the advanced CKD and ESRD populations.

The strengths of our study include its examination of a large cohort of incident ESRD patients with both pre-ESRD and post-ESRD data; comprehensive availability of information on prescription data, comorbidities, laboratory tests, pain severity, and clinical events; and reduced confounding on the basis of differential health care access and non-uniform medical care by receiving care within the VA healthcare system. Yet several limitations of our study should be acknowledged. First, given the retrospective nature of our study, we were not able to precisely determine the indications for which opiate and non-opiate analgesics were prescribed (i.e., nociceptive vs. neuropathic pain)[15], nor if analgesics were administered for conditions other than pain (i.e., epilepsy, pruritis); however, upon examining pre-existing conditions associated with opiate use in our multivariable models (i.e., neuropathy), we observed robust associations between pre-ESRD opiate use and post-ESRD death. Second, due to data limitations we were unable to ascertain use of analgesics outside of the VA healthcare system (i.e., over-the-counter, prescription from non-VA providers), nor the type of analgesic prescribers (i.e., primary care, nephrology, etc.). Third, our examination of pre-ESRD analgesic status and post-ESRD mortality does not convey information about opiate use and short-term death risk, nor did our analyses include those who maintained stable kidney function, experienced death or underwent kidney transplantation prior to dialysis initiation, or those who declined dialysis. However, as prior studies have demonstrated an association between opiate use and short-term mortality risk in dialysis patients, our intention was to specifically examine the long-term impact of opiate use in the pre-ESRD period upon post-ESRD mortality. Fourth, as the study cohort was restricted to US Veterans, our findings may have limited generalizability to populations with differing case-mix characteristics. Lastly, as with all observational studies, residual confounding cannot be excluded, and our findings do not confirm a causal association between opiate analgesic use and mortality risk.

In summary, our study shows that incident ESRD patients with opiate analgesic use during the pre-ESRD prelude period have higher post-ESRD mortality, and this risk is increasingly stronger with greater frequency of opiate use. Among non-opiate analgesics, we also found that pre-ESRD gabapentin/pregabalin use was associated with higher post-ESRD death. Further studies are needed to define safe and effective pharmacologic and non-pharmacologic interventions that can optimally manage chronic pain in advanced CKD patients transitioning to ESRD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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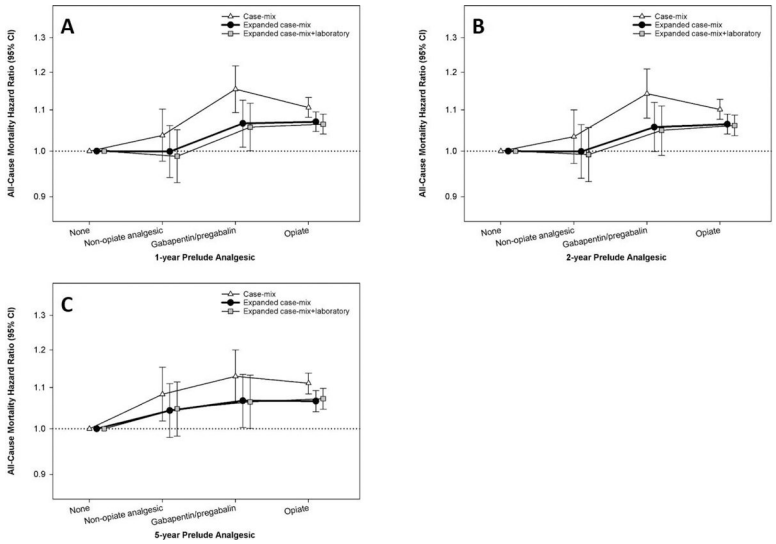

Fig. 1. Pre-end-stage renal disease (ESRD) opiate, gabapentin/pregabalin, other non-opiate analgesic, and no analgesic use and post-ESRD mortality risk in the one-year (Panel A), two-year (Panel B), and five-year (Panel C) prelude cohorts (ref: no analgesic use).

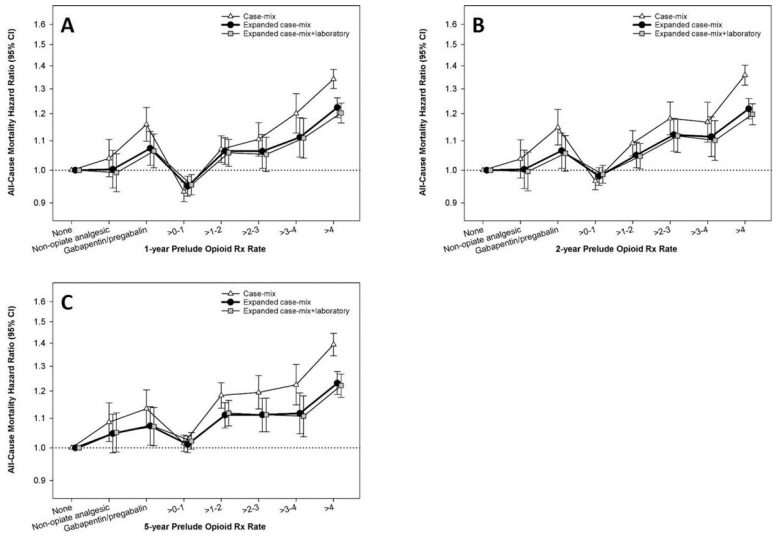

Fig. 2. Pre-end-stage renal disease (ESRD) frequency of opiate prescription and post-ESRD mortality risk in the one-year (Panel A), two-year (Panel B), and five-year (Panel C) prelude cohorts (ref: no analgesic use).

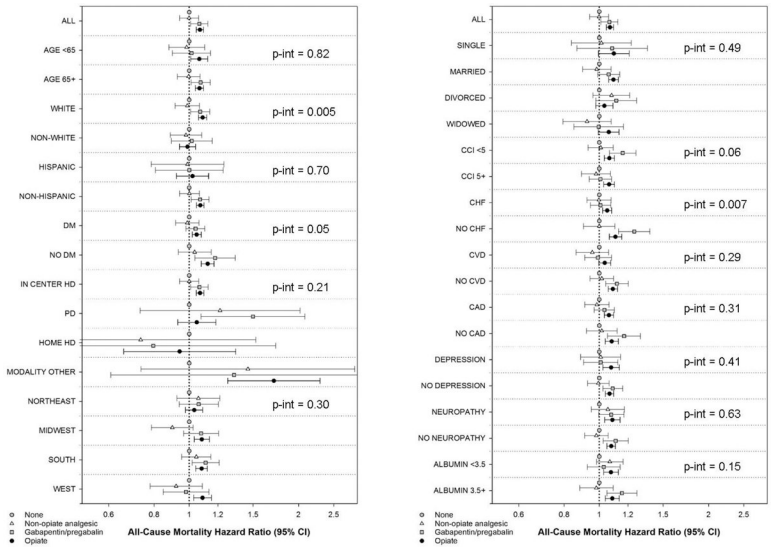

Fig. 3. Pre-end-stage renal disease (ESRD) opiate, gabapentin/pregabalin, other non-opiate analgesic, and no analgesic use and post-ESRD mortality risk across clinically relevant subgroups in the one-year prelude cohort (ref: no analgesic use).

Analyses adjusted for expanded case-mix covariates. Abbrev.: DM, diabetes; HD, hemodialysis; PD, peritoneal dialysis; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CVD, cerebrovascular disease; CAD, coronary artery disease.

Table 1.

Baseline characteristics stratified by pre-end-stage renal disease (ESRD) opiate, other non-opiate analgesic use, gabapentin/pregabalin use, vs. no analgesic use in the one-year prelude cohort.

	PRE-ESRD ANALGESIC USE STATUS					
	Overall	**None**	**Non-opiate analgesic**	**Gabapentin/ pregabalin**	**Opiate analgesic**	**P-value**
N (%)	57764	24519 (42)	2108 (4)	2458 (4)	28679 (50)	-
Age, years (mean ± SD)	71 ± 11	73 ± 11	69 ± 12	71 ± 10	69 ± 11	<0.001
Female (%)	4	3	2	4	5	<0.001
Race (%)						<0.001
White	71	76	53	77	68	
Black	24	20	41	18	27	
Other	5	4	5	5	5	
Hispanic ethnicity (%)	6	6	8	9	7	<0.001
Marital status (%)						<0.001
Single	7	7	12	7	8	
Married	59	64	45	63	55	
Divorced	22	18	29	20	26	
Widowed	11	12	13	11	10	
Region (%)						<0.001
Northeast	17	21	18	17	14	
Midwest	23	24	21	24	22	
South	42	39	46	43	44	
West	18	16	14	15	20	
Cause of ESRD (%)						<0.001
Diabetes	44	40	43	57	46	
Hypertension	31	35	31	23	29	
Glomerulonephritis	6	6	6	3	6	
Cystic disease	1	1	0.3	0.5	1	
Other urologic cause	1	1	2	1	1	
Other cause	11	11	9	9	10	
Unknown cause/missing	6	6	8	5	6	
Initial dialysis modality (%)						<0.001
In center HD	93	93	96	94	93	
PD	5	5	2	4	6	
Home HD	1	1	1	1	1	
Other/missing	1	2	1	1	1	
Comorbidities						
CCI, median (IQR)	4 (2, 6)	4 (2, 6)	4 (2, 5)	5 (3, 6)	4 (2, 6)	<0.001
Diabetes (%)	67	64	66	83	69	<0.001
CHF (%)	56	55	54	63	55	<0.001
CAD (%)	59	61	52	66	58	<0.001

	PRE-ESRD ANALGESIC USE STATUS					
	Overall	**None**	**Non-opiate analgesic**	**Gabapentin/ pregabalin**	**Opiate analgesic**	**P-value**
CVD (%)	31	33	29	37	30	<0.001
Depression (%)	23	16	24	28	28	<0.001
Neuropathy (%)	30	20	36	58	37	<0.001
Pain score, median (IQR)	0.8 (0.0, 2.4)	0.0 (0.0, 1.0)	0.7 (0.2, 1.7)	0.7 (0.0, 2.3)	1.6 (0.4, 3.3)	<0.001
Laboratory results, median (IQR)						
Serum albumin, 1-year averaged (g/dL)	3.5 (3.1, 3.8)	3.6 (3.2, 3.9)	3.3 (2.9, 3.7)	3.5 (3.1, 3.9)	3.4 (3.0, 3.8)	<0.001
eGFR, 1-year averaged (ml/min/1.73m^2)	16.0 (11.9, 23.9)	16.4 (11.7, 25.0)	14.6 (11.0, 20.9)	18.5 (13.9, 27.4)	15.8 (11.9, 23.1)	<0.001
eGFR, at dialysis initiation (ml/min/1.73m^2)	12.6 (8.6, 19.7)	13.9 (9.3, 22.3)	10.8 (7.4, 16.0)	14.9 (10.4, 23.9)	11.8 (8.2, 17.9)	<0.001

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; CHF, congestive heart failure; CAD, coronary artery disease; CVD, cerebrovascular disease; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate.