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Sumida, Keiichi
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Laxative use in patients with advanced chronic kidney disease transitioning to dialysis

Keiichi Sumida[1], Ankur A. Dashputre[1,2], Praveen K. Potukuchi[1,2], Fridtjof Thomas[3], Yoshitsugu Obi[1], Miklos Z. Molnar [1,4,5,6], Justin D. Gatwood[7], Elani Streja[8], Kamyar Kalantar-Zadeh[8] and Csaba P. Kovesdy [1,9]

[1]Department of Medicine, Division of Nephrology, University of Tennessee Health Science Center, Memphis, TN, USA, [2]College of Graduate Health Sciences, Institute for Health Outcomes and Policy, University of Tennessee Health Science Center, Memphis, TN, USA, [3]Department of Preventive Medicine, Division of Biostatistics, College of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA, [4]James D. Eason Transplant Institute, Methodist University Hospital, Memphis, TN, USA, [5]Department of Surgery, Division of Transplant, University of Tennessee Health Science Center, Memphis, TN, USA, [6]Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary, [7]Department of Clinical Pharmacy and Translational Science, College of Pharmacy, University of Tennessee Health Science Center, Nashville, TN, USA, [8]Division of Nephrology and Hypertension, Harold Simmons Center for Chronic Disease Research and Epidemiology, University of California-Irvine, Orange, CA, USA and [9]Nephrology Section, Memphis VA Medical Center, Memphis, TN, USA

Correspondence to: Csaba P. Kovesdy; E-mail: ckovesdy@uthsc.edu

ORIGINAL ARTICLE

ABSTRACT

Background. Constipation is highly prevalent in patients with chronic kidney disease (CKD), particularly among those with end-stage renal disease (ESRD), partly due to their dietary restrictions, comorbidities and medications. Laxatives are typically used for constipation management; however, little is known about laxative use and its associated factors in patients with advanced CKD transitioning to ESRD.

Methods. In a retrospective cohort of 102 477 US veterans transitioning to dialysis between October 2007 and March 2015, we examined the proportion of patients who filled a prescription for any type of laxative within each 6-month period over 36 months pre- and post-transition to ESRD. Factors associated with laxative use during the last 1-year pre-ESRD period were identified by multivariable logistic regression.

Results. The proportion of patients prescribed laxatives increased as patients progressed to ESRD, peaking at 37.1% in the 6 months immediately following ESRD transition, then remaining fairly stable throughout the post-ESRD transition period. Among laxative users, stool softeners were the most commonly prescribed (~30%), followed by hyperosmotics (~20%), stimulants (~10%), bulk formers (~3%), chloride channel activator (<1%) and several combinations of these. The use of anticoagulants, oral iron supplements, non-opioid analgesics, antihistamines and opioid analgesics were among the factors independently associated with pre-ESRD laxative use.

Conclusion. The use of laxatives increased considerably as patients neared transition to ESRD, likely mirroring the increasing burden of drug-induced constipation during the ESRD transition period. Findings may provide novel insight into better

management strategies to alleviate constipation symptoms and reduce medication requirements in patients with advanced CKD.

Keywords: chronic kidney disease, constipation, end-stage renal disease, laxative, transition

INTRODUCTION

Constipation is the prototype of functional gastrointestinal disorders and one of the most prevalent conditions encountered in daily clinical practice [1]. Approximately 30% of the general population experiences problems with constipation during their lifetime, with women and elderly people being most affected [2]. In patients with chronic kidney disease (CKD), especially in its advanced stages, the prevalence of constipation is reported to be higher than in the general population [3–5], presumably due in part to their dietary restrictions (e.g. limited fiber and/or fluid intake), comorbidities, concomitant medications and altered gut microbiota [6–11]. Because of these predisposing factors, nonpharmacological treatments such as increased fiber supplements and physical activity may not always be practical and effective, and pharmacological interventions are often required for the management of constipation in this particular population [12].

Currently, a wide range of pharmacological agents are available, including commonly used laxative compounds (e.g. bulk formers, hyperosmotics, stimulants, stool softeners and lubricants) and relatively new laxatives with more physiological mechanisms of action (e.g. chloride channel activators,

KEY LEARNING POINTS

What is already known about this subject?

- constipation is highly prevalent in patients with chronic kidney disease (CKD), particularly among those with end-stage renal disease (ESRD) receiving dialysis;
- pharmacological interventions are often required for the management of constipation in advanced CKD patients, and a wide range of laxative agents are currently available; and
- however, information is scarce on the prevalence and patterns of laxative use and its associated factors in patients with advanced CKD transitioning to ESRD.

What this study adds?

- the use of laxatives increased considerably (up to ∼37%) as patients progressed to ESRD, and remained fairly stable after the transition to ESRD;
- the use of anticoagulants, oral iron supplements, non-opioid analgesics, antihistamines and opioid analgesics were among the factors independently associated with laxative use during the last 1-year period before transition to ESRD; and
- these results are likely mirroring the increasing burden of drug-induced constipation during the ESRD transition period, which may provide novel insight into better management strategies to alleviate constipation symptoms and reduce medication requirements in patients with advanced CKD.

What impact this may have on practice or policy?

- the high prevalence of laxative use in advanced CKD may help raise the awareness of prevalent constipation in this population, along with its contribution to health and economic burden;
- the identification of the medications associated with pre-ESRD laxative use may help detect previously under-recognized causes of drug-induced constipation and can help avoid unnecessary or inappropriate use of laxatives along with their unwanted adverse effects; and
- the potential changes in practice habits to avoid unnecessary laxative use could contribute to a lower overall pill and economic burden in this relevant population.

guanylate cyclase C-receptor agonists, selective serotonin 5-HT_4 receptor agonists and ileal bile acid transporter inhibitors) [13, 14], some of which have been shown to have unique reno-protective properties [15–17]. Despite these therapeutic advances, no practice guidelines currently exist for constipation management in CKD; thus physicians may supposedly base their treatments largely on their clinical experience or habitual practice, which can sometimes be wasteful and harmful to patients [18]. Furthermore, the costs related to laxative administration (e.g. drug cost, pharmacy management and downstream investigations for laxative-induced adverse effects) are estimated to be strikingly high, contributing substantially to healthcare financial burden [19–21].

Given these problems with laxative use and the exceptionally high health and economic burden in patients with advanced CKD transitioning to end-stage renal disease (ESRD) [22], it is vital to better understand the real-world practice patterns of laxative use during this critical transition period toward efforts to improve patient-centered care and outcomes. However, information is scarce on the prevalence and patterns of laxative use in patients with advanced CKD. We therefore aimed to describe the prevalence and patterns of laxative use during the 36-month pre- and post-ESRD transition periods, and further examined the clinical factors independently associated with pre-ESRD laxative use.

MATERIALS AND METHODS

Study population

We analyzed longitudinal data from the US Renal Data System (USRDS) Transition of Care in CKD study, a nationally representative retrospective cohort study of US veterans who transitioned to ESRD [23–25]. In this study, a total of 102 477 US veterans who transitioned to ESRD from 1 October 2007 through 31 March 2015 were identified from the USRDS as a source population. In order to describe the trend in laxative use during the transition period (as detailed in the next subsection), we first identified 20 127 patients who had at least one prescription record for any medication within each 6-month time period over 36-months pre- and post-transition to ESRD. Prescribed medications were ascertained using both inpatient and outpatient prescriptions sourced from Centers for Medicare and Medicaid Services (CMS) Medicare Part D and Veterans Affairs (VA) pharmacy dispensation records [26].

For identifying factors associated with pre-ESRD laxative use, we separately identified 70 128 patients with at least one prescription for any medication during the last 1-year prior to dialysis initiation. In order to stringently define the laxative users and non-laxative users for this aim, we selected 11 667 out of 70 128 patients who had at least two laxative prescriptions 30 days apart during the 1-year pre-ESRD period (i.e. laxative

users). Among the remaining 58 461 patients, we additionally identified 34 965 patients who did not have any laxative prescription during the entire pre-ESRD period and defined these as comparators (i.e. non-laxative users), resulting in the final analytical population of 46 632 patients (Supplementary data, Figure S1). Compared with patients in the final analytical population, those who were excluded from the analysis (i.e. $n = 23\,496$) were younger, less likely to be married and more likely to be African American and use medications (Supplementary data, Table S1).

Laxative use prevalence and patterns

Laxative use during the transition period was described as the proportion of patients who used any type of laxative, which was defined as the ratio of the number of patients who filled at least one prescription of any laxative (i.e. numerator) to the 20 127 patients identified to have at least one prescription medication (i.e. denominator) within each 6-month period over the 36-month pre- and post-ESRD transition periods. Laxative agents were ascertained according to prescription information for the following six types of laxatives: stool softeners, hyperosmotics, stimulants, bulk formers, chloride channel activator and lubricants (Supplementary data, Table S2). Among patients with at least one laxative prescription, the proportion of each or combination of these types of laxatives was assessed for each 6-month period over the 72-month evaluation period. All proportions were reported as percentages. The relationship between the number of different types of laxatives and the number of prescribed drugs was additionally examined among patients with at least one prescription medication in the last 6-month pre-ESRD period.

Covariates

Patient demographic characteristics, including age, sex, and self-identified race and ethnicity, were ascertained from the following three national databases: the USRDS, VA and CMS. Data on marital status, smoking status and service connectivity (a measure indicating whether one or more of a patient's comorbidities were caused by their military service, resulting in certain privileges, such as preferential access to care and lower copayments) were obtained from VA records only [27, 28]. Preexisting comorbidities were identified from the VA Inpatient and Outpatient Medical SAS Datasets, using the International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic and procedure codes and Current Procedural Terminology codes, as well as from VA/CMS data [29]. The Charlson comorbidity index (CCI) score was calculated using the Deyo modification for administrative datasets, without including kidney disease [30]. Cardiovascular disease was defined as the presence of diagnostic codes for coronary artery disease, angina, myocardial infarction or cerebrovascular disease [31]. Bowel disorders were defined as the presence of diagnostic codes for inflammatory bowel disease, irritable bowel syndrome or diarrhea. Laboratory data were obtained from the VA research databases as previously described [32, 33], and their baseline values were defined as the average of each laboratory test during the 2-year baseline period

(vide infra). Similarly, patients with at least one prescription over the 2-year baseline period were recorded as having been treated with the medication. Estimated glomerular filtration rate (eGFR) was calculated with the CKD Epidemiology Collaboration creatinine equation using outpatient serum creatinine and demographic data [34]. Intraindividual slope of eGFR was calculated using a linear mixed-effects model using all outpatient eGFR values available in the 2-year baseline period and, given the potential non-linear association of eGFR slope with laxative use, stratified into four *a priori* categories (i.e. less than -10, -10 to less than -5, -5 to <0 and ≥ 0 mL/min/1.73 m^2/year) for the analysis [25].

Statistical analysis

Baseline patient characteristics were summarized by laxative users ($n = 11\,667$) and non-laxative users ($n = 34\,965$) and presented as number (percentages) for categorical variables and mean [standard deviation (SD)] for continuous variables with a normal distribution or median [interquartile range (IQR)] for those with a skewed distribution. In order to account for the temporality of the association between baseline clinical characteristics and laxative use status and not to miss the potential short-term effects of factors that might affect subsequent use of laxatives, the baseline was defined based on the 2-year time period immediately prior to the first date of laxative prescription during the last 1-year pre-ESRD period among laxative users. Among non-laxative users, the 2-year baseline period was anchored by an index date of 296 days prior to dialysis initiation, which corresponded to the median time interval from the first date of laxative prescription to dialysis initiation in laxative users.

We performed multivariable logistic regression to identify factors independently associated with laxative use during the last 1-year pre-ESRD period. Based on theoretical consideration and the availability in this study, the following variables were included in the main adjusted model: demographics [age, sex, race and marital status), smoking status, service connectivity, comorbidities (diabetes, hyperlipidemia, cardiovascular disease, congestive heart failure, cerebrovascular disease, lung disease, connective tissue disease, peptic ulcer disease, liver disease, human deficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), malignancy, anemia, atrial fibrillation, depression and bowel disorders], CCI, medications [renin–angiotensin system inhibitors, β-blockers, calcium channel blockers, diuretics, phosphate binders (calcium acetate, sevelamer or lanthanum), sodium polystyrene sulfonate, antidepressants, non-opioid analgesics, opioids, antihistamines, anticholinergics, antiarrhythmics, anticoagulants, antipsychotics, anti-Parkinson drugs, antacids, anticonvulsants and oral iron supplements] and cumulative length of hospitalizations over the 2-year baseline period. Of the variables included in the multivariable model, data points were missing for race (0.01%), marital status (5.4%), service connectivity (1.9%), comorbidities (0.8%) and medications (7.6%). Of the 46 632 patients in the analytical cohort, 39 578 (88.7%) had complete data available for the multivariable model.

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Due to the relatively high proportion of missing information for body mass index (BMI; 33.3%), systolic blood pressure (30.4%), last eGFR and eGFR slope during the 2-year baseline period (37.7%), these variables were additionally included in the main model as a sensitivity analysis, which resulted in 57.8% of the population in the analytical cohort. A two-sided P < 0.05 was used as a threshold of statistical significance for all analyses. Due to the large sample size, the significance of differences in baseline characteristics by laxative use status was established based on considerations of biologically or clinically meaningful differences. All analyses were conducted in SAS Enterprise guide version 7.1 (SAS Institute, Cary, NC, USA) and STATA/MP version 15 (STATA Corporation, College Station, TX, USA). The study was approved by the Institutional Review Boards of the Memphis and Long Beach VA Medical centers, with exemption from informed consent.

RESULTS

Laxative use during the transition period

Within each 6-month period over the entire 72-month transition period, the proportion of patients with at least one laxative prescription ranged from 17.5% to 37.1% (Supplementary data, Table S3). As depicted in Figure 1, the use of laxatives gradually increased as patients progressed to ESRD, with a marked increase seen in the 6 months immediately prior to ESRD transition. Laxative use peaked in the first 6 months following dialysis initiation and remained fairly stable at ∼30% throughout the post-ESRD period (Figure 1). The proportion of patients who had continuous laxative prescriptions throughout the entire transition period was 2.8%.

Among patients with at least one laxative prescription, the majority (≥55%) was prescribed a single type of laxative throughout the transition period, with stool softeners being the most commonly prescribed (25.8–31.5%), followed by hyperosmotics (16.9–20.8%), stimulants (8.8–11.7%), bulk formers (1.3–4.3%) and chloride channel activator (0–0.02%) (Figure 2 and Supplementary data, Table S4). There was a decreasing trend in the overall proportion of patients who used a single type of laxative over time, with a marked temporary drop seen in the 6 months immediately before and after the ESRD transition. A corresponding increase in the overall proportion of combined use of laxatives was observed. Among different laxative types, stool softeners, hyperosmotics and stimulants were commonly used in combination with each other (Figure 2 and Supplementary data, Table S4). There was a graded relationship between the number of different types of laxatives and the number of prescribed drugs (Supplementary data, Table S5).

Factors associated with laxative use

In a total of 46 632 patients included in this analysis, baseline characteristics overall and in those categorized by laxative use status are shown in Table 1. The overall mean (SD) age was 72.5 (11.3) years; 95.2% of patients were male; 22.7% were African American; and 72.9% were diabetic. The mean baseline eGFR was 32.5 mL/min/1.73 m^2. Compared with nonlaxative users, laxative users were younger, more likely to be African American, a current smoker and service connected, and less likely to be married. They had a higher prevalence of diabetes as a primary cause of ESRD and comorbidities except cerebrovascular disease, connective tissue disease, peptic ulcer disease, malignancy and atrial fibrillation, and also had longer cumulative length of hospitalization during the 2-year baseline period. The use of medications except calcium channel blockers was more common among laxative users.

Figure 3 shows the factors independently associated with pre-ESRD laxative use in descending order of the magnitude of the odds ratio (OR). In the multivariable-adjusted model, the use of certain medications such as anticoagulants [OR 4.24, 95% confidence interval (CI) 3.88–4.63], oral iron supplements (3.42, 95% CI 3.17–3.69), non-opioid analgesics (2.51, 95% CI 2.34–2.69), antihistamines (2.47, 95% CI 2.15–2.84) and opioid analgesics (2.11, 95% CI 1.98–2.23) were among the strongest factors positively associated with pre-ESRD laxative use. African American (versus white) race and the presence of anemia (OR 1.35, 95% CI 1.24–1.47), depression (1.32, 95% CI 1.16–1.49) and liver disease (1.11, 95% CI 1.03–1.20) were also associated with pre-ESRD laxative use. Meanwhile, married (versus unmarried) status (OR 0.69, 95% CI 0.65–0.73) and certain comorbidities such as HIV/AIDS (0.56, 95% CI 0.42–0.76), connective tissue disease (0.69, 95% CI 0.62–0.77) and hyperlipidemia (0.74, 95% CI 0.68–0.82) were negatively associated with pre-ESRD laxative use (Figure 3).

Factors significantly associated with pre-ESRD laxative use were fairly similar after additional adjustment for BMI, systolic blood pressure, last eGFR and eGFR slope in a sensitivity analysis. Of note, eGFR slopes less than −10 and ≥0 (versus −5 to <0) mL/min/1.73 m^2/year were both associated with pre-ESRD laxative use (ORs 1.56, 95% CI 1.35–1.81 and 1.41, 95% CI 1.28–1.54, respectively) (Supplementary data, Figure S2). The odds of pre-ESRD laxative use associated with all examined variables are summarized in Supplementary data, Table S6.
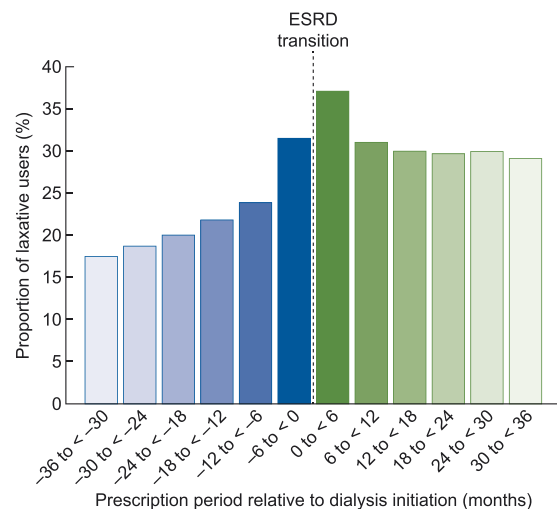

FIGURE 1: Proportion of laxative use within each 6-month period over 36 months pre- and post-ESRD transition.
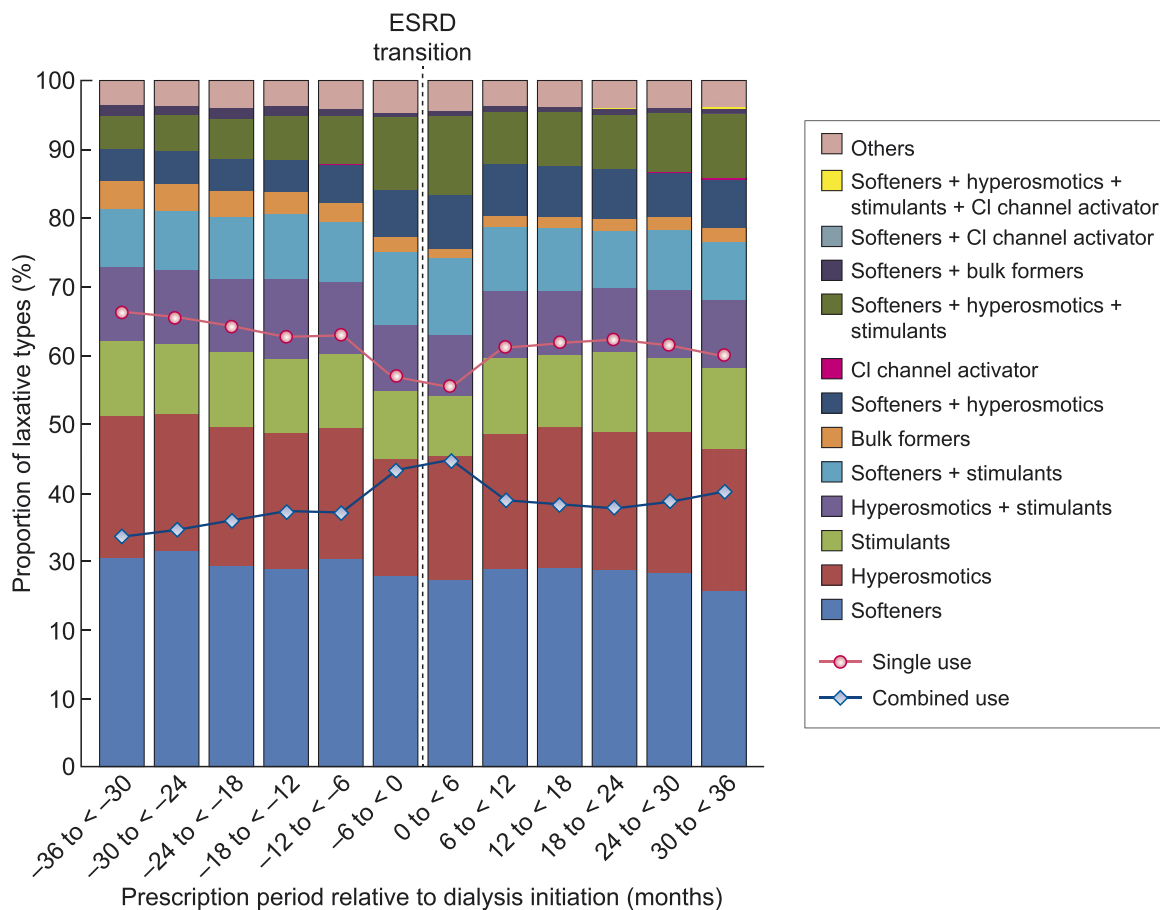
FIGURE 2: Proportion of laxative types used alone or in combination among patients with at least one laxative prescription within each 6-month period over 36 months pre- and post-ESRD transition. Solid (red) and dotted (blue) lines represent single and combined use of laxatives, respectively.

DISCUSSION

In this large national cohort of US veterans transitioning to dialysis, we described the patterns of laxative use during 36 months pre- and post-transition to ESRD and identified clinical factors associated with pre-ESRD laxative use. Laxative use increased as patients progressed to ESRD, peaked at 37.1% in the first 6 months following dialysis initiation and remained fairly stable thereafter throughout the post-ESRD period. While the majority of laxatives were used alone, with stool softeners (∼30% of all laxatives), hyperosmotics (∼20%) and stimulants (∼10%) being most commonly prescribed, there was an increasing trend in combined use of laxatives over time, peaking at ∼45% in the 6 months immediately before and after the transition to ESRD. The use of medications, such as anticoagulants, oral iron supplements, non-opioid analgesics, antihistamines and opioid analgesics, was associated with higher odds of pre-ESRD laxative use.

Several studies have examined the prevalence of laxative use and reported its wide variation ranging from 6 to 67% depending on the studied population, including the general population [35], community-dwelling elderly [36], hospitalized patients [20] and people living in nursing homes [37]. However, as with the paucity of data on the prevalence of constipation among patients with advanced stages of CKD, information on the prevalence of laxative use in the advanced CKD population is very

limited. In a recent study including 21 patients with nondialysis-dependent CKD (NDD-CKD) with eGFR <15 mL/min/1.73 m^2, 98 on hemodialysis and 21 on peritoneal dialysis, the prevalence of self-reported laxative use was 23.8, 30.6 and 42.9%, respectively [38]. The study also showed that, among different types of laxatives, docusate (a stool softener) was the most commonly used laxative in all patient groups [38]. In another study investigating the relationship between laxative use and clinical parameters among 136 hemodialysis patients, 66.2% of them used laxatives, and female sex, older age, diabetes and hyperhomocysteinemia were shown to be independently associated with laxative use [39]. These studies, however, were small in size and cross-sectional, focusing separately on NDD-CKD or ESRD populations. In this study, we therefore extended the previous observations to a large and unique cohort of patients with advanced NDD-CKD transitioning to dialysis, and for the first time described temporal changes in laxative use during the ESRD transition period and identified various factors independently associated with pre-ESRD laxative use.

Patients with CKD typically suffer from an immense burden of medications, comorbidities, metabolic abnormalities and altered gut microbiota, particularly in the most advanced stages of CKD [8, 40], all of which are suggested as predisposing factors for constipation [12]. In line with this evidence, our results showed a sustained increase in laxative use as patients

Table 1. Baseline patient characteristics overall and stratified by laxative use status during the year prior to dialysis transition among 46 632 patients in the analytical cohort

Characteristic	Total (N = 46 632)	Laxative users (n = 11 667)	Non-laxative users (n = 34 965)
Age, mean (SD), year	72.5 (11.3)	68.5 (10.4)	73.8 (11.3)
Male sex, n (%)	44 374 (95.2)	11 264 (96.5)	33 110 (94.7)
Race, n (%)			
White	34 528 (74.0)	7165 (61.4)	27 363 (78.3)
African American	10 586 (22.7)	4126 (35.4)	6460 (18.5)
Others	1515 (3.3)	376 (3.2)	1139 (3.2)
Married, n (%)	27 278 (58.5)	5675 (48.6)	21 603 (61.8)
Smoking status, n (%)			
Current	12 221 (26.2)	4352 (37.3)	7869 (22.5)
Past	13 401 (28.7)	3581 (30.7)	9820 (28.1)
Never	11 268 (24.2)	3284 (28.2)	7984 (22.8)
Unknown	9742 (20.9)	450 (3.8)	9292 (26.6)
Service connected, n (%)	15 109 (32.4)	5828 (49.9)	9281 (26.5)
Systolic BP, mean (SD), mmHg	141.7 (16.1)	142.7 (14.7)	141.2 (16.8)
BMI, mean (SD), kg/m^2	29.4 (6.1)	30.2 (6.7)	28.9 (5.8)
Primary cause of ESRD, n (%)			
Diabetes	19 736 (42.3)	5776 (49.5)	13 960 (39.9)
Hypertension	15 061 (32.3)	2920 (25.0)	12 141 (34.7)
Glomerulonephritis	2546 (5.5)	580 (5.0)	1966 (5.6)
Cystic kidney disease	564 (1.2)	110 (1.0)	454 (1.3)
Other urologic condition	660 (1.4)	141 (1.2)	519 (1.5)
Other cause	5148 (11.0)	1285 (11.0)	3863 (11.1)
Missing	2917 (6.3)	855 (7.3)	2062 (5.9)
Renal replacement modality, n (%)			
Hemodialysis	38 224 (81.9)	9890 (84.8)	28 334 (81.0)
Peritoneal dialysis	2511 (5.4)	464 (3.9)	2047 (5.9)
Other/uncertain	5713 (12.3)	1260 (10.8)	4453 (12.7)
Missing	184 (0.4)	53 (0.5)	131 (0.4)
Comorbidities, n (%)			
Diabetes	33 980 (72.9)	9277 (79.5)	24 703 (70.6)
Hypertension	45 049 (96.6)	11 485 (98.4)	33 564 (95.9)
Hyperlipidemia	39 578 (84.9)	10 030 (85.9)	29 458 (84.5)
Cardiovascular disease	36 066 (77.3)	9265 (79.4)	26 801 (76.7)
Congestive heart failure	30 870 (66.2)	7972 (68.3)	22 898 (65.5)
Cerebrovascular disease	21 542 (46.2)	5209 (44.6)	16 333 (46.7)
Lung disease	26 300 (56.4)	7018 (60.2)	19 282 (55.2)
Connective tissue disease	4100 (8.8)	826 (7.1)	3274 (9.4)
Peptic ulcer disease	5425 (11.6)	1386 (11.9)	4039 (11.6)
Liver disease	9043 (19.4)	2763 (23.7)	6280 (17.9)
HIV/AIDS	494 (1.1)	172 (1.5)	322 (0.9)
Malignancies	15 242 (32.7)	3761 (32.2)	11 481 (32.8)
Anemia	37 926 (81.3)	10 173 (87.2)	27 753 (79.4)
Atrial fibrillation	13 032 (27.9)	2883 (24.7)	10 149 (29.0)
Depression	13 827 (29.6)	5257 (45.1)	8570 (24.5)
Bowel disorders[a]	12 038 (25.8)	3176 (27.2)	8862 (25.4)
CCI, median (IQR)	5 (3,7)	5 (4,7)	5 (3,7)
Cumulative length of hospitalization, median (IQR), days	0 (0,7)	4 (0,16)	0 (0,5)
Medications, n (%)			
RASi	28 390 (60.9)	8758 (75.1)	19 632 (56.5)
β-blockers	30 186 (64.7)	9338 (80.0)	20 848 (59.6)
Calcium channel blockers	27 352 (58.7)	8459 (30.9)	18 893 (54.0)
Diuretics	31 350 (67.2)	9926 (85.1)	21 424 (61.3)
Phosphate binders	4226 (9.1)	2168 (18.6)	2058 (5.9)
Sodium polystyrene sulfonate	4483 (9.6)	2289 (19.6)	2194 (6.3)
Antidepressants	12 529 (26.9)	5216 (44.7)	7313 (20.9)
Non-opioid analgesics	7386 (15.8)	4758 (40.8)	2628 (7.5)
Opioids	18 997 (40.7)	7545 (64.7)	11 452 (32.8)
Anticholinergics	3875 (8.3)	1827 (15.7)	2048 (5.9)
Antihistamines	1984 (4.3)	1553 (13.3)	431 (1.2)
Antiarrhythmics	2123 (4.6)	635 (5.4)	1488 (4.3)
Anticoagulants	5265 (11.3)	4040 (34.6)	1225 (3.5)
Antipsychotics	2246 (4.8)	1252 (10.7)	994 (2.8)
Anti-Parkinson drugs	1189 (2.5)	346 (2.9)	843 (2.4)

Continued

Table 1. Continued

Characteristic	Total ($N = 46\,632$)	Laxative users ($n = 11\,667$)	Non-laxative users ($n = 34\,965$)
Antacids	3444 (7.4)	2253 (19.3)	1191 (3.4)
Anticonvulsants	8397 (18.0)	3667 (31.4)	4730 (13.5)
Oral iron supplements	6147 (13.2)	4311 (36.9)	1836 (5.3)
Laboratory parameters			
eGFR, mean (SD), mL/min/1.73 m^2	32.5 (18.8)	33.0 (19.4)	32.2 (18.5)
Last eGFR, mL/min/1.73 m^2	28.7 (19.0)	27.6 (19.4)	29.4 (18.8)
eGFR slope, n (%)			
Less than -10 mL/min/1.73 m^2/year	5862 (12.6)	2895 (24.8)	2967 (8.5)
-10 to <-5 mL/min/1.73 m^2/year	9229 (19.8)	3177 (27.2)	6052 (17.3)
-5 to <0 mL/min/1.73 m^2/year	12 411 (26.6)	3873 (33.2)	8538 (24.4)
≥ 0 mL/min/1.73 m^2/year	1552 (3.3)	752 (6.5)	800 (2.3)

Data are presented as number (percentage), mean (SD) or median (IQR). All P-values except peptic ulcer disease and anti-Parkinson drugs for between-group comparison were statistically significant.

[a]Bowel disorders include inflammatory bowel disease, irritable bowel syndrome and diarrhea.

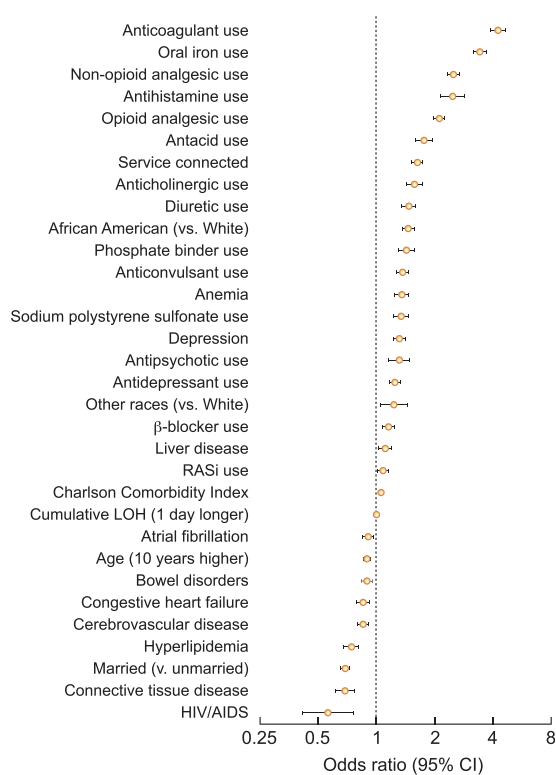RASi, renin–angiotensin system inhibitor.

FIGURE 3: Factors independently associated with pre-ESRD laxative use. Pre-ESRD laxative use was defined as at least two laxative prescriptions 30-days apart during the 1-year pre-ESRD period.

progressed to ESRD, with a marked increase seen in the 6 months immediately preceding dialysis initiation. A similar increase observed in the combined use of laxatives might additionally suggest that the severity of constipation symptoms also increased with worsening kidney function during the pre-ESRD period. In this context, our findings regarding the factors associated with pre-ESRD laxative use may be of particular value, with potential clinical and research implications. Among various clinical characteristics, the majority of factors significantly associated with pre-ESRD laxative use were the use of medications, most of which are known to induce constipation as a side effect (e.g. oral iron, opioid analgesics and anticholinergics)

[12]. Although it is unclear why the use of anticoagulants, which themselves seem unlikely to significantly affect gastrointestinal motility, showed the strongest association with pre-ESRD laxative use, it is possible that patients with anticoagulant use were prescribed laxatives for the purpose of preventing bleeding complications associated with constipation (e.g. lower gastrointestinal bleeding) [41, 42], albeit we cannot conclude any causal relationship. It is also possible that patients on warfarin adjust their diet to limit foods high in vitamin K, which could lead to constipation. The identification of these medications may help detect previously under-recognized causes of drug-induced constipation and, perhaps more importantly, can help avoid unnecessary or inappropriate use of laxatives along with their unwanted adverse effects. Specifically, for those taking both iron supplements and laxatives, for example, switching from oral to intravenous iron supplementation might be helpful to ameliorate their symptom of constipation and reduce laxative requirements. These changes in practice habits could also contribute to a lower overall pill burden in this relevant population. Whether the use of laxatives has any beneficial effects beyond conventional defecation management in this unique population (e.g. disposal of uremic toxins, maintaining mineral homeostasis or retaining commensal gut microbiota) may deserve further investigation.

Despite the advantages of this study including its large sample size of patients with advanced CKD, our results must be interpreted in light of some limitations. Most of our patients were male US veterans, and hence results may not apply to women or patients from other geographic areas. Information about over-the-counter use of laxatives was not available; therefore, it is possible that we underestimated the proportion of patients with laxative use and/or misclassified those who used only over-the-counter laxatives as nonlaxative users. It is also important to note that the use of laxatives did not necessarily reflect a person's constipation status, especially given the lack of information about subjective symptoms of constipation and the fact that only a minority of patients with constipation seek medical care [43]. In addition, prescription does not necessarily mean that patients actually took the drugs. Lastly, as with all observational studies, we cannot eliminate the possibility of

unmeasured confounders (e.g. diet and lifestyle) that might have potentially affected pre-ESRD laxative use.

In conclusion, laxative use increased considerably as patients progressed to ESRD and remained fairly stable after the transition to ESRD, likely mirroring the increasing burden of drug-induced constipation during the ESRD transition period. Although further studies are needed to identify optimal practice patterns in the use of laxatives, our findings may provide novel insight into better management strategies to alleviate constipation symptoms and reduce medication requirements in patients with advanced CKD, potentially contributing to the improvement of patient-centered care and outcomes in this population.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

AUTHORS' CONTRIBUTIONS

K.S., A.A.D., P.K.P., F.T. and C.P.K. were responsible for study concept and design. K.S., A.A.D., P.K.P., M.Z.M., E.S., K.K.-Z. and C.P.K. were involved in data acquisition. K.S., A.A.D. and P.K.P. carried out data analyses. K.S., A.A.D., P.K.P., F.T., Y.O., M.Z.M., J.D.G., E.S., K.K.-Z. and C.P.K. were involved in data interpretation. K.K.-Z. and C.P.K. supervised the study. Each author contributed important intellectual content during manuscript drafting or revision and agreed to be accountable for all aspects of the work in ensuring that questions pertaining to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors reviewed and approved the final version of this manuscript.

CONFLICT OF INTEREST STATEMENT

None of the authors has relevant conflicts of interest.

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