Prevalence of Opioid, Gabapentinoid, and NSAID Use in Patients with CKD

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Over 60% of individuals with CKD have chronic pain, a prevalence two to three times that of the general population (1). Although the pharmacologic treatment of pain among individuals with normal kidney function is often challenging, pain management in people with CKD is even more complicated (1). Nonsteroidal anti-inflammatory drugs (NSAIDs) may be contraindicated in those with CKD (1). Although opioids may lack the direct nephrotoxicity of NSAIDs, nearly all undergo at least partial excretion by the kidneys (2). Gabapentinoids (gabapentin and pregabalin) are alternative therapeutic options, but they also rely primarily on excretion through the kidneys (3,4). Little is known regarding the prevalence of prescription opioid use among patients with CKD; how this compares with other analgesics, such as gabapentinoids and NSAIDs; and how prevalence compares with that in individuals with normal kidney function.

We assessed the prevalence of prescriptions for opioids (including tramadol, methadone and buprenorphine), gabapentinoids, and NSAIDs (excluding aspirin and topical formulations) across stages of kidney function in primary care patients using the Geisinger Health System, a large rural health system in Pennsylvania, and Johns Hopkins Medicine, a large health system in Maryland. We chose two populations to explicitly evaluate geographic differences in prescribing patterns and CKD prevalence (5). We included all patients over age 18 years old with at least one outpatient measure of serum creatinine between 2011 and 2016 at Geisinger and between 2013 and 2016 at Johns Hopkins Medicine. The study was deemed exempt by the Geisinger Medical Center Institutional Review Board and the Johns Hopkins University School of Medicine.

A period prevalence cohort was created for each calendar year in Geisinger and Johns Hopkins Medicine including all eligible individuals with at least one outpatient creatinine measure. We defined opioid, gabapentinoid, and NSAID use as electronic medical record documentation of at least one outpatient prescription or patient self-report at any point during the calendar year. We used the first annual outpatient serum creatinine value and the Chronic Kidney Disease Epidemiology Collaboration equation to calculate eGFR (6). Individuals were categorized into CKD stages according to the Kidney Disease Improving Global Outcomes (KDIGO) guideline (7). We calculated the proportion of individuals who received at least one opioid, gabapentinoid, or NSAID prescription within each CKD stage between January 1 and December 31. Prevalence ratios were estimated adjusting for age, sex, and race. All analyses were performed using Stata version 14.2 (StataCorp, College Station, TX).

In total, 333,049 patients had at least one serum creatinine measured between 2011 and 2016 in the Geisinger cohort, and 188,403 patients had at least one serum creatinine measured between 2013 and 2016 in the Johns Hopkins Medicine cohort. In 2016, there were 181,107 and 109,219 patients in Geisinger and Johns Hopkins Medicine, respectively, and 31.8% and 22.7% received at least one prescription for an opioid, respectively (Table 1). Adjusting for demographics, patients with CKD stage G4/G5 were 40% more likely than those with CKD stage G1 to receive an opioid prescription in Geisinger and 90% more likely to receive a prescription in Johns Hopkins Medicine. Among those with CKD stage G4/G5, crude prevalence increased over time in both Geisinger and Johns Hopkins Medicine cohorts ($P<0.001$).

Gabapentin and pregabalin prescriptions were less common in the overall cohort: at 9.9% and 6.3% of the Geisinger and Johns Hopkins Medicine cohorts in 2016, respectively. Similar to opioid prescriptions, gabapentinoids were more common among patients with lower eGFR, and prescriptions among patients with stage G4/G5 CKD in particular increased over time.

Overall, NSAID use was similar across the two cohorts. In contrast to opioids and gabapentinoids, NSAID use was lower in patients with lower eGFR in both cohorts. Trends in NSAID use over time were more variable.

Several limitations bear mention. The study describes medication use in two large cohorts, and it was not designed to make therapeutic recommendations by level of eGFR or investigate whether pain medications cause CKD. Medication exposure was determined using electronic medical records, and it may not be a true reflection of use. We may have missed over-the-counter NSAID use and prescriptions from providers outside the Geisinger and Johns Hopkins Medicine systems. We only adjusted for demographic

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Table 1. Population characteristics and crude and adjusted prevalence and prevalence ratios of opioid, gabapentinoid, and nonsteroidal anti-inflammatory drug prescriptions at Geisinger Health System and Johns Hopkins Medicine in 2016

Characteristic/Outcome	2016 Geisinger Health System,[a] *n*=181,107			2016 Johns Hopkins Medicine,[a] *n*=109,219		
	Opioids[b,c]	Gabapentinoid[c]	NSAIDs[c]	Opioids[b,c]	Gabapentinoid[c]	NSAIDs[c]
Population characteristics						
Age, yr, mean (SD)	59 (17)	59 (16)	54 (16)	57 (15)	58 (14)	53 (15)
Women, %	61	62	62	63	65	65
Black, %	3	3	3	35	36	37
Crude period prevalence, %						
Total	31.8	11.2	27.1	22.7	7.8	25.2
G1	31.7	10.8	32.6	20.4	6.5	27.2
G2	29.6	10.5	26.8	21.9	7.6	25.3
G3	35.9	13.2	18.0	31.4	12.6	19.1
G4/G5[d]	49.0	16.9	7.8	48.7	17.3	7.6
Adjusted period prevalence,[e] % (95% CI)						
Total	29.1 (28.7 to 29.5)	9.9 (9.7 to 10.1)	27.1 (26.5 to 27.7)	19.7 (19.3 to 20.1)	6.3 (6.1 to 6.5)	19.0 (18.6 to 19.4)
G1	33.0 (32.4 to 33.6)	12.1 (11.7 to 12.5)	23.6 (23.2 to 24.0)	21.2 (20.4 to 22.0)	7.4 (6.8 to 8.0)	21.4 (20.6 to 22.2)
G2	26.4 (26.0 to 26.8)	8.9 (8.7 to 9.1)	20.2 (19.2 to 21.2)	18.3 (17.7 to 18.9)	5.6 (5.2 to 6.0)	20.1 (19.5 to 20.7)
G3	35.6 (34.6 to 36.6)	13.9 (13.1 to 14.7)	6.7 (5.3 to 8.1)	27.6 (26.0 to 29.2)	10.6 (9.6 to 11.6)	18.6 (17.2 to 20.0)
G4/G5[d]	55.2 (52.3 to 58.1)	20.1 (17.7 to 22.5)	22.7 (22.3 to 23.1)	46.4 (41.7 to 51.1)	14.8 (11.5 to 18.1)	10.1 (7.2 to 13.0)
Adjusted prevalence ratios,[e] % (95% CI)						
G1	Reference	Reference	Reference	Reference	Reference	Reference
G2	0.9 (0.9 to 0.9)	0.9 (0.9 to 1.0)	0.9 (0.9 to 1.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.1)	1.0 (1.0 to 1.0)
G3	1.0 (1.0 to 1.1)	1.1 (1.1 to 1.2)	0.7 (0.7 to 0.7)	1.3 (1.2 to 1.3)	1.4 (1.3 to 1.5)	0.7 (0.7 to 0.8)
G4/G5[d]	1.4 (1.4 to 1.5)	1.4 (1.3 to 1.6)	0.3 (0.3 to 0.3)	1.9 (1.8 to 2.1)	1.9 (1.7 to 2.2)	0.3 (0.2 to 0.3)

NSAID, nonsteroidal anti-inflammatory drug; 95% CI, 95% confidence interval.

[a]In 2016, the total Geisinger population had a mean (SD) age of 57.6 (17.5) years old, 57.0% were women, and 2.5% were black. At Johns Hopkins Medicine, mean (SD) age was 54.1 (16.1) years old, 59.1% were women, and 29.2% were black.

[b]The percentage of patients in 2016 who had record of prescription opioids for methadone and buprenorpine was 0.9% at Geisinger and 0.3% at Johns Hopkins Medicine.

[c]Serum creatinine measurement and prescription documentation were not necessarily concomitant. Median time between creatinine measurement and prescription was 65 days in both cohorts for opioids; 74 and 77 days for gabapentinoids in Geisinger and Johns Hopkins, respectively; and 75 and 82 days for NSAIDs in Geisinger and Johns Hopkins, respectively.

[d]Individuals receiving dialysis were included in this category. Individuals with a history of kidney transplant were categorized according to their eGFR at the time that serum creatinine was measured.

[e]Adjusted for age, sex, and race. Adjusted period prevalence estimates are shown for a white man age 60 years old.

variables without taking into account pain chronicity, severity, or etiology, and the relationship between increased prescriptions at lower eGFR may reflect a higher burden of comorbidities. Creatinine measurement and prescription were not necessarily concomitant. Finally, prescription trends over time were assessed in period prevalent cohorts, with overlap in the study population from year to year.

Using real world clinical data from two large tertiary health care systems, we report that prescriptions for opioids and gabapentinoids were common in patients with advanced CKD. Differences between the two cohorts may reflect the geographic variability in opioid prescriptions across the United States (5). Our findings highlight the need for heightened awareness regarding opioid and gabapentinoid use in the CKD population as well as additional studies to determine the safety of such medications in clinical practice.

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G.C.A. is Chair of the Food and Drug Administration's Peripheral and Central Nervous System Advisory Committee; serves as a paid advisor to IQVIA; serves on the advisory board of MesaRx Innovations; holds equity in Monument Analytics, a health care consultancy with clients that include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

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