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Perioperative Gabapentin Use and In-Hospital Adverse Clinical Events Among Older Adults After Major Surgery

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IMPORTANCE Gabapentin has been increasingly used as part of a multimodal analgesia regimen to reduce opioid use in perioperative pain management. However, the safety of perioperative gabapentin use among older patients remains uncertain.

OBJECTIVE To examine in-hospital adverse clinical events associated with perioperative gabapentin use among older patients undergoing major surgery.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study using data from the Premier Healthcare Database included patients aged 65 years or older who underwent major surgery at US hospitals within 7 days of hospital admission from January 1, 2009, to March 31, 2018, and did not use gabapentin before surgery. Data were analyzed from June 14, 2021, to May 23, 2022.

EXPOSURES Gabapentin use within 2 days after surgery.

MAIN OUTCOMES AND MEASURES The primary outcome was delirium, identified using diagnosis codes, and secondary outcomes were new antipsychotic use, pneumonia, and in-hospital death between postoperative day 3 and hospital discharge. To reduce confounding, 1:1 propensity score matching was performed. Risk ratios (RRs) and risk differences (RDs) with 95% CIs were estimated.

RESULTS Among 967 547 patients before propensity score matching (mean [SD] age, 76.2 [7.4] years; 59.6% female), the rate of perioperative gabapentin use was 12.3% (119 087 patients). After propensity score matching, 237 872 (118 936 pairs) gabapentin users and nonusers (mean [SD] age, 74.5 [6.7] years; 62.7% female) were identified. Compared with nonusers, gabapentin users had increased risk of delirium (4040 [3.4%] vs 3148 [2.6%]; RR, 1.28 [95% CI, 1.23-1.34]; RD, 0.75 [95% CI, 0.75 [0.61-0.89] per 100 persons), new antipsychotic use (944 [0.8%] vs 805 [0.7%]; RR, 1.17 [95% CI, 1.07-1.29]; RD, 0.12 [95% CI, 0.05-0.19] per 100 persons), and pneumonia (1521 [1.3%] vs 1368 [1.2%]; RR, 1.11 [95% CI, 1.03-1.20]; RD, 0.13 [95% CI, 0.04-0.22] per 100 persons), but there was no difference in in-hospital death (362 [0.3%] vs 354 [0.2%]; RR, 1.02 [95% CI, 0.88-1.18]; RD, 0.00 [95% CI, −0.04 to 0.05] per 100 persons). Risk of delirium among gabapentin users was greater in subgroups with high comorbidity burden than in those with low comorbidity burden (combined comorbidity index <4 vs ≥4: RR, 1.20 [95% CI, 1.13-1.27] vs 1.40 [95% CI, 1.30-1.51]; RD, 0.41 [95% CI, 0.28-0.53] vs 2.66 [95% CI, 2.08-3.24] per 100 persons) and chronic kidney disease (absence vs presence: RR, 1.26 [95% CI, 1.19-1.33] vs 1.38 [95% CI, 1.27-1.49]; RD, 0.56 [95% CI, 0.42-0.69] vs 1.97 [95% CI, 1.49-2.46] per 100 persons).

CONCLUSION AND RELEVANCE In this cohort study, perioperative gabapentin use was associated with increased risk of delirium, new antipsychotic use, and pneumonia among older patients after major surgery. These results suggest careful risk-benefit assessment before prescribing gabapentin for perioperative pain management.

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Multimodal analgesia has been an increasingly adopted strategy in the Enhanced Recovery After Surgery pathway,[1] which aims to reduce opioid use by using nonopioid analgesia, such as regional or epidural analgesia, nonsteroidal anti-inflammatory drugs, acetaminophen, and gabapentinoids.[2] Randomized clinical trials (RCTs) have demonstrated that multimodal analgesia improves pain control[3-5] and decreases opioid use and its adverse effects.[2-7] The American Pain Society recommends gabapentin as a component of multimodal analgesia.[8] Although the contribution of perioperative gabapentin use to the overall population trend remains unknown, gabapentin use tripled from 2002 to 2015 and has been the 10th most prescribed drug in the US since 2016.[9,10]

Despite the widespread use of gabapentin, recent studies raised concerns about the marginal benefit and immediate harms of gabapentin use for perioperative pain management.[11] Studies,[12-14] including meta-analyses of RCTs, concluded that the evidence on gabapentin's effectiveness is low quality owing to inconsistent and imprecise results and that its analgesic and opioid-sparing effects may be clinically insignificant. Moreover, perioperative gabapentin use was associated with dizziness and visual disturbances.[13] Although there were no statistically significant differences in perioperative delirium, respiratory failure, ataxia, or falls,[13] the studies did not exclude the possibility of clinically meaningful adverse events owing to small sample sizes, underrepresentation of older patients, and heterogenous surgical procedures. The American Geriatrics Society Beers Criteria[15] lists gabapentin as a potentially inappropriate medication owing to its risk of sedation and respiratory depression, especially when used with opioids. Because older surgical patients are vulnerable to these adverse effects and are at increased risk of perioperative delirium, pneumonia, and death, there is a need to examine the safety of perioperative gabapentin use using a health care database of the general population that includes a large number of older adults undergoing different types of surgical procedures.

We conducted a retrospective cohort study to investigate the association of perioperative gabapentin use with in-hospital adverse clinical events using a nationwide administrative inpatient database of older adults undergoing major surgery. We hypothesized that gabapentin use would be associated with increased risk of delirium, pneumonia, and in-hospital death.

Key Points

Question Is perioperative gabapentin use associated with in-hospital adverse clinical events among older adults after major surgery?

Findings In this cohort study of 237 872 propensity score–matched adults aged 65 years or older, perioperative gabapentin users had significantly increased risk of delirium, new antipsychotic use, and pneumonia compared with nonusers after major surgery.

Meaning This study suggests that careful risk-benefit assessment is needed before prescribing gabapentin for perioperative pain management to older patients.

Methods

Data Source

This retrospective cohort study using the Premier Healthcare Database was approved by the institutional review board of Brigham and Women's Hospital, and a waiver of informed consent was obtained because the data were deidentified. The Premier Healthcare Database is a deidentified, hospital-based, service-level, all-payer database containing more than 900 small-sized to medium-sized hospitals that covers approximately 25% of annual inpatient admissions in the US. The database contains information on demographic characteristics, admission status, diagnosis codes, discharge status, and date-stamped records of drugs and procedures. This nationwide database has been used to investigate the safety of medical interventions in the inpatient care setting.[16-18] This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Population

The analytic sample included adults aged 65 years or older who underwent major surgical procedures within 7 days of hospital admission from January 1, 2009, to March 31, 2018. Major surgical procedures included cardiac, gastrointestinal, genitourinary, orthopedic, neurological (excluding procedures involving the brain), thoracic, and vascular surgery, as defined by the Agency for Healthcare Research and Quality procedure classification.[19,20] We excluded patients who died or were discharged before or on postoperative day 2 because we defined gabapentin use based on the exposure on the day of surgery or on postoperative days 1 or 2 (exposure-defining period). Because gabapentin is typically started before surgery and continued postoperatively, we refer to this regimen as perioperative use. We also excluded patients who had diagnosis codes for psychosis, received antipsychotics before or on postoperative day 2, received gabapentin before the day of surgery, or had diagnosis codes for other potential indications for gabapentin (alcohol use disorder, alcohol withdrawal, fibromyalgia, neuropathic pain, postherpetic neuralgia, restless legs syndrome, seizure, and social anxiety disorder) or contraindications to gabapentin (myasthenia gravis). Moreover, patients who received critical care, mechanical ventilation, or a feeding tube before or on postoperative day 2 were excluded because they had a higher acuity of illness and were unlikely to receive gabapentin orally.

Measurement of Perioperative Gabapentin Use and Covariates

We defined perioperative gabapentin use based on charge codes, which identify each service item (eg, medications and procedures) for billing and reimbursement purposes, on the day of surgery or postoperative day 1 or 2. We calculated total daily gabapentin dose (in milligrams) given during the exposure-defining period. To avoid immortal time bias,[21] the group that used gabapentin and the group that did not use gabapentin were required to have survived the exposure-defining period.

The following patient-level characteristics were assessed: age, sex, race and ethnicity (Black, White, or other [American Indian, Asian/Pacific Islander, Hispanic, and other]), insurance type (commercial, Medicare, Medicaid, or other), admission type (elective, urgent, emergent, or other) and source (outpatient, emergency department, transfer, or other), surgery type (cardiac, gastrointestinal, genitourinary, orthopedic, neurological, thoracic, or vascular), combined comorbidity index (scores range from −2 to 26, with higher scores indicating greater risk of death),[22] and comorbidity diagnoses. Race and ethnicity were obtained from Uniform Billing Code of 1992 billing forms. Inpatient medication use, including analgesics (acetaminophen, cyclooxygenase-2 inhibitors, nonsteroidal anti-inflammatory drugs, and opioid use and dose in morphine milligram equivalent [MME] per day), and receipt of cardiopulmonary resuscitation, dialysis, or blood transfusion before surgery and during the first 2 postoperative days were measured. We also obtained hospital bed capacity, teaching status, location (urban or rural), and geographic region. To account for changes in gabapentin-prescribing patterns and surgical outcomes over time, we recorded calendar year of the hospital admission.

Study Outcomes

The primary outcome was delirium, identified using a validated claims-based algorithm.[23,24] This algorithm, which consists of explicit (ie, delirium is directly mentioned) and implicit (eg, encephalopathy) diagnosis codes of delirium (eTable 1 in the Supplement), has a positive predictive value of 80% against the Confusion Assessment Method, as validated in a previous study of 184 patients.[23] As secondary outcomes, we assessed (1) new antipsychotic use, which has a positive predictive value of 92% for delirium[23]; (2) pneumonia, which was defined based on diagnosis codes plus intravenous antibiotic use or computed tomography of the chest; and (3) in-hospital death. Analogous to the intention-to-treat analysis in an RCT, patients were followed up from postoperative day 3 until the occurrence of the outcomes or hospital discharge regardless of the presence or duration of gabapentin therapy.

Statistical Analysis

Data were analyzed from June 14, 2021, to May 23, 2022. To reduce confounding, we performed propensity score matching.[25,26] A propensity score was estimated as the probability of receiving gabapentin from a logistic regression model that included all patient- and hospital-level characteristics. We conducted 1:1 nearest-neighbor matching and assessed covariate balance based on the standardized mean difference (<0.1 was considered adequate).[25] We estimated risk ratios (RRs), risk differences (RDs), and 95% CIs for delirium, new antipsychotic use, pneumonia, and in-hospital death associated with gabapentin use. We also examined the association in subgroups defined by age (<80 or ≥80 years), sex, comorbidity burden (combined comorbidity index <4 or ≥4), chronic kidney disease status (presence or absence), opioid dose (MME<15 mg per day or ≥15 mg per day), and surgery type (cardiac, gastrointestinal, genitourinary, orthopedic, neurological, thoracic, or vascular). Within each subgroup, we reestimated the propensity score, and performed 1:1 matching; we tested heterogeneity across subgroups.[27] Two-sided $P < .05$ for heterogeneity was considered significant. We performed 3 sensitivity analyses regarding (1) gabapentin exposure present on the day of surgery, (2) dose-response relationship, and (3) unmeasured confounding. First, we repeated the analysis by defining gabapentin exposure on the day of surgery without requiring a 2-day minimum length of stay after surgery. Then, we explored a dose-response relationship using a 4-dose category of gabapentin (no use, 1 mg to <600 mg, 600 mg to <1200 mg, or ≥1200 mg). Because 4-group propensity score matching was not feasible, we used multivariable logistic regression models to adjust for covariates selected by a stepwise algorithm with a 2-sided P value threshold of 0.10 for entry and removal of a covariate from the model. In addition, because pain intensity may be an unmeasured confounder of the association between gabapentin use and delirium, we examined how the RR estimate would change under various scenarios: (1) the prevalence difference in severe pain between gabapentin users and nonusers and (2) the relative risk between severe pain and delirium from the literature (severe perioperative pain was associated with a 1.2-fold increase in delirium).[28] Analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Results

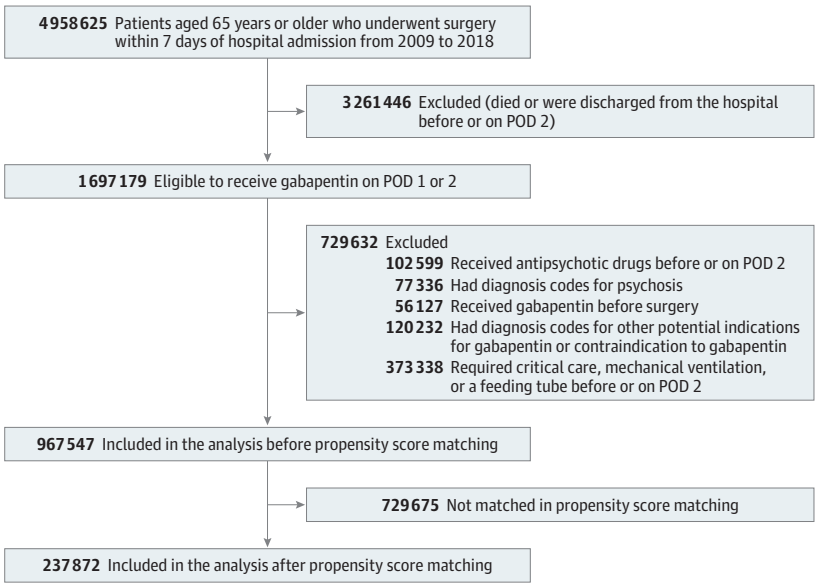
Characteristics of Study Population

After applying inclusion and exclusion criteria, 967 547 patients (mean [SD] age, 76.2 [7.4] years; 59.6% female) were eligible to initiate gabapentin for perioperative pain management (**Figure 1**). Of these patients, 119 087 (12.3%; mean [SD] age, 74.5 [6.7] years; 62.7% female) received gabapentin between the day of surgery (108 190 [90.8%]) and 2 days after surgery. The most common surgery type among gabapentin users was orthopedic (91 014 [76.4%]). Compared with those who did not use gabapentin, gabapentin users were younger (mean [SD] age, 74.5 [6.7] vs 76.4 [7.5] years), were more likely to be female (74 627 [62.7%] vs 501 934 [59.2%]), underwent more elective surgical procedures (93 674 [78.7%] vs 422 262 [49.8%]), and had a lower comorbidity index (mean [SD], 1.2 [2.2] vs 1.8 [2.6]). However, gabapentin users were more frequently treated with analgesics, including opioids (109 389 [91.9%] vs 686 293 [80.9%]), a higher daily opioid dose (mean [SD], 7.6 [6.1] MME vs 5.8 [5.6] MME), and psychoactive drugs, such as antidepressants (29 772 [25.0%] vs 141 942 [16.7%]) and anxiolytics (84 529 [71.0%] vs 525 736 [62.0%]) (**Table 1**; the complete covariate list is given in eTable 2 in the Supplement). After 1:1 propensity score matching, we identified 237 872 (118 936 pairs) gabapentin user and nonusers. Baseline characteristics were well balanced (standardized mean difference, <0.1) in the propensity score–matched cohort (Table 1).

Adverse Clinical Events Associated With Perioperative Gabapentin Use

Before propensity score matching, gabapentin users had lower risk of adverse clinical events than nonusers (**Table 2**). After

Figure 1. Flowchart of Study Population Selection



POD indicates postoperative day.

propensity score matching, gabapentin users had increased risk (RR and RD) of delirium (4040 [3.4%] vs 3148 [2.6%]; RR, 1.28 [95% CI, 1.23-1.34]; RD, 0.75 [95% CI, 0.61-0.89] per 100 persons), new antipsychotic use (944 [0.8%] vs 805 [0.7%]; RR, 1.17 [95% CI, 1.07-1.29]; RD, 0.12 [95% CI, 0.05-0.19] per 100 persons), and pneumonia (1521 [1.3%] vs 1368 [1.2%]; RR, 1.11 [95% CI, 1.03-1.20]; RD, 0.13 [95% CI, 0.04-0.22] per 100 persons) compared with nonusers. In-hospital death was similar between gabapentin users and nonusers (362 [0.3%] vs 354 [0.2%]; RR, 1.02 [95% CI, 0.88-1.18]; RD, 0.00 [95% CI, -0.04 to 0.05] per 100 persons).

Subgroup Analyses

Across the subgroups defined by age, sex, comorbidity burden, chronic kidney disease status, and opioid dose, the associations of gabapentin use with delirium, new antipsychotic use, and pneumonia were consistent (**Figure 2** and **Figure 3**). The RR of delirium was greater among gabapentin users younger than 80 years than among those aged 80 years or older (1.34 [95% CI, 1.27-1.43] vs 1.21 [95% CI, 1.12-1.30]; $P = .02$ for heterogeneity), but the RD was similar (0.71 [95% CI, 0.57-0.86] vs 0.91 [95% CI, 0.56-1.27] per 100 persons; $P = .31$ for heterogeneity). The RR and RD were greater among patients with high comorbidity burden (≥4) than among those with low comorbidity burden (<4) (RR, 1.40 [95% CI, 1.30-1.51] vs 1.20 [95% CI, 1.13-1.27]; $P = .001$ for heterogeneity; RD, 2.66 [95% CI, 2.08-3.24] vs 0.41 [95% CI, 0.28-0.53] per 100 persons; $P < .001$ for heterogeneity) and among patients with chronic kidney disease (absence vs presence: RR, 1.26 [95% CI, 1.19-1.33] vs 1.38 [95% CI, 1.27-1.49]). Subgroup estimates differed only on the RD scale for risk of delirium by chronic kidney disease status (absence vs presence: RD, 0.56 [95% CI, 0.42-0.69] vs 1.97 [95% CI, 1.49-2.46] per 100 persons; $P < .001$ for heterogeneity), risk of new antipsychotic use by comorbidity burden (<4 vs ≥4: 0.09 [95% CI, 0.03-0.15] vs 0.65 [0.33-0.97] per 100 persons; $P = .001$ for heterogeneity), and risk of pneumonia by comorbidity burden (<4 vs ≥4: 0.15 [95% CI, 0.07-0.22] vs 0.66 [0.25-1.07] per 100 persons; $P = .02$ for heterogeneity) and chronic kidney disease status (absence vs presence: 0.14 [95% CI, 0.06-0.23] vs 0.47 [95% CI, 0.17-0.77] per 100 persons; $P = .04$ for heterogeneity). There was no statistically significant evidence for heterogeneity by sex or opioid dose on the RR or RD scale. Because of the small number of clinical events, certain surgery-specific estimates were imprecise, but in general, the associations were consistent with increased risk of outcomes with gabapentin use (eTable 3 in the Supplement). Perioperative gabapentin use was not associated with in-hospital death in all subgroups.

Sensitivity Analyses

When gabapentin exposure was defined on the day of surgery without requiring a minimum 2-day length of stay after surgery, the results were unchanged from our primary analysis (eTable 4 in the Supplement). On multivariable logistic regression analysis (eTable 5 in the Supplement), increasing gabapentin dose was associated with progressively increased risk of delirium diagnosis (1 mg to <600 mg: adjusted odds ratio [AOR], 1.25 [95% CI, 1.18-1.32]; 600 mg to <1200 mg: AOR, 1.30 [95% CI, 1.24-1.36]; ≥1200 mg: AOR, 1.43 [95% CI, 1.28-1.60]) and pneumonia (1 mg to <600 mg: AOR, 1.05 [95% CI, 0.96-1.14]; 600 mg to <1200 mg: AOR, 1.16 [95% CI, 1.07-1.25]; ≥1200 mg: AOR, 1.34 [95% CI, 1.13-1.59]) but not with new antipsychotic use and in-hospital death. In a sensitivity analysis for unmeasured confounding (eFigure in the Supplement), we found that the RR of 1.28 in our study would become null if (1) the prevalence difference of severe pain was at least 30% between the treatment groups or (2) the RR between severe pain and delirium was at least 2.0, which was greater than previously reported in the literature (ie, >2.0).[28] These results suggest that unmeasured, severe pain alone is unlikely to explain our results.

Table 1. Characteristics of Patients by Perioperative Gabapentin Use Before and After Propensity Score Matching

Characteristic	Before propensity score matching			After propensity score matching[a]		
	Gabapentin use (n = 119 087)[b]	No gabapentin use (n = 848 460)[b]	SMD	Gabapentin use (n = 118 936)[b]	No gabapentin use (n = 118 936)[b]	SMD
Age, mean (SD), y	74.5 (6.7)	76.4 (7.5)	−0.27	74.5 (6.7)	74.4 (6.8)	0.01
Sex						
Female	74 627 (62.7)	501 934 (59.2)	0.07	74 525 (62.7)	74 682 (62.8)	<0.01
Male	44 460 (37.3)	346 526 (40.8)	−0.07	44 411 (37.3)	44 254 (37.2)	<0.01
Race and ethnicity						
Black	9231 (7.8)	62 406 (7.4)	0.01	9215 (7.7)	9274 (7.8)	<0.01
White	98 562 (82.8)	697 010 (82.2)	0.02	98 438 (82.8)	98 490 (82.8)	<0.01
Other[c]	11 294 (9.5)	89 044 (10.5)	−0.03	11 283 (9.5)	11 172 (9.4)	<0.01
Insurance type						
Medicare	106 860 (89.7)	764 277 (90.1)	−0.01	106 727 (89.7)	106 931 (89.9)	−0.01
Medicaid	1704 (1.4)	10 998 (1.3)	0.01	1699 (1.4)	1618 (1.4)	0.01
Commercial	8115 (6.8)	58 163 (6.9)	<0.01	8106 (6.8)	8078 (6.8)	<0.01
Other	1270 (1.1)	7806 (0.9)	0.01	1269 (1.1)	1213 (1.0)	<0.01
Uninsured	1138 (1.0)	7216 (0.9)	0.01	1135 (1)	1096 (0.9)	<0.01
Hospital admission type						
Elective	93 674 (78.7)	422 262 (49.8)	0.63	93 523 (78.6)	94 096 (79.1)	−0.01
Urgent	7368 (6.2)	85 342 (10.1)	−0.14	7368 (6.2)	7258 (6.1)	<0.01
Emergent	16 780 (14.1)	327 675 (38.6)	−0.58	16 780 (14.1)	16 256 (13.7)	0.01
Other	1265 (1.1)	13 181 (1.6)	−0.04	1265 (1.1)	1326 (1.1)	<0.01
Surgery type						
Cardiac	624 (0.5)	16 391 (1.9)	−0.13	624 (0.5)	556 (0.5)	0.01
Gastrointestinal	15 866 (13.3)	195 395 (23.0)	−0.25	15 863 (13.3)	15 249 (12.8)	0.02
Genitourinary	2523 (2.1)	48 933 (5.8)	−0.19	2523 (2.1)	2461 (2.1)	<0.01
Neurological	3096 (2.6)	12 085 (1.4)	0.08	3088 (2.6)	3217 (2.7)	−0.01
Orthopedic	91 014 (76.4)	498 258 (58.7)	0.39	90 875 (76.4)	91 315 (76.8)	−0.01
Thoracic	1549 (1.3)	20 288 (2.4)	−0.08	1549 (1.3)	1585 (1.3)	<0.01
Vascular	4415 (3.7)	57 110 (6.7)	−0.14	4414 (3.7)	4553 (3.8)	−0.01
CCI score, mean (SD)[d]	1.2 (2.2)	1.8 (2.6)	−0.24	1.2 (2.2)	1.1 (2.2)	0.01
Comorbidities						
Any tumor	13 798 (11.6)	137 070 (16.2)	−0.13	13 788 (11.6)	13 474 (11.3)	0.01
Chronic pulmonary disease	25 542 (21.4)	180 276 (21.2)	<0.01	25 490 (21.4)	25 196 (21.2)	0.01
Congestive heart failure	12 625 (10.6)	121 638 (14.3)	−0.11	12 607 (10.6)	12 551 (10.6)	<0.01
Dementia	3311 (2.8)	49 664 (5.9)	−0.15	3310 (2.8)	3149 (2.6)	0.01
Kidney failure	2846 (2.4)	45 468 (5.4)	−0.15	2846 (2.4)	2856 (2.4)	<0.01
Analgesic drugs						
Acetaminophen	102 013 (85.7)	598 803 (70.6)	0.37	101 867 (85.6)	102 237 (86.0)	−0.01
Cyclooxygenase-2 inhibitor	24 837 (20.9)	65 370 (7.7)	0.38	24 764 (20.8)	24 432 (20.5)	0.01
NSAID	26 822 (22.5)	124 966 (14.7)	0.20	26 771 (22.5)	26 921 (22.6)	<0.01
Opioid	109 389 (91.9)	686 293 (80.9)	0.32	109 238 (91.8)	109 561 (92.1)	−0.01
Opioid dose, MME/d, mean (SD)	7.6 (6.1)	5.8 (5.6)	0.31	7.6 (6.1)	7.7 (6.3)	<0.01
Psychoactive drugs						
Alzheimer disease agents	2943 (2.5)	29 494 (3.5)	−0.06	2942 (2.5)	2831 (2.4)	0.01
Antidepressants	29 772 (25.0)	141 942 (16.7)	0.20	29 659 (24.9)	29 720 (25.0)	<0.01
Anxiolytics	84 529 (71.0)	525 736 (62.0)	0.19	84 411 (71.0)	84 662 (71.2)	<0.01
Sedatives	7805 (6.6)	42 346 (5.0)	0.07	7784 (6.5)	7762 (6.5)	<0.01
Hospital characteristic						
Teaching	55 930 (47.0)	367 537 (43.3)	0.07	55 843 (47.0)	55 577 (46.7)	<0.01
Urban	107 083 (89.9)	750 848 (88.5)	0.05	106 944 (89.9)	106 680 (89.7)	0.01

(continued)

Table 1. Characteristics of Patients by Perioperative Gabapentin Use Before and After Propensity Score Matching (continued)

Characteristic	Before propensity score matching			After propensity score matching[a]		
	Gabapentin use (n = 119 087)[b]	No gabapentin use (n = 848 460)[b]	SMD	Gabapentin use (n = 118 936)[b]	No gabapentin use (n = 118 936)[b]	SMD
Geographic region						
Northeast	27 825 (23.4)	182 705 (21.5)	0.04	27 776 (23.4)	27 529 (23.1)	<0.01
Midwest	18 704 (15.7)	135 019 (15.9)	-0.01	18 690 (15.7)	18 639 (15.7)	<0.01
South	50 055 (42.0)	382 716 (45.1)	-0.06	50 006 (42.0)	50 672 (42.6)	-0.01
West	22 503 (18.9)	148 020 (17.4)	0.04	22 464 (18.9)	22 096 (18.6)	0.01

Abbreviations: CCI, combined comorbidity index; MME, morphine milligram equivalent; NSAID, nonsteroidal anti-inflammatory drug; SMD, standardized mean difference.

[a] The propensity score model included demographic information, insurance type, admission characteristics, surgery type, combined comorbidity score, comorbidities, inpatient medication use and procedures before or on postoperative day 2, hospital-level characteristics, geographic region, and calendar year.

[b] Data are reported as number (percentage) of patients unless otherwise indicated.

[c] Included individuals who identified as American Indian, Asian/Pacific Islander, Hispanic, or other.

[d] Scores range from −2 to 26, with higher scores indicating greater risk of death.

Table 2. Association Between Perioperative Gabapentin Use and In-Hospital Adverse Clinical Events After Major Surgery Before and After Propensity Score Matching

Outcome	Before propensity score matching				After propensity score matching[a]			
	Gabapentin use, No. (%) (n = 119 087)	No gabapentin use, No. (%) (n = 848 460)	RR (95% CI)	RD, per 100 persons (95% CI)	Gabapentin use, No. (%) (n = 118 936)	No gabapentin use, No. (%) (n = 118 936)	RR (95% CI)	RD, per 100 persons (95% CI)
Delirium diagnosis	4051 (3.4)	34 342 (4.0)	0.84 (0.81 to 0.87)	-0.6 (-0.8 to -0.5)	4040 (3.4)	3148 (2.6)	1.28 (1.23 to 1.34)	0.75 (0.61 to 0.89)
New antipsychotic use	945 (0.8)	9877 (1.2)	0.68 (0.64 to 0.73)	-0.4 (-0.4 to -0.3)	944 (0.8)	805 (0.7)	1.17 (1.07 to 1.29)	0.12 (0.05 to 0.19)
Pneumonia	1522 (1.3)	19 902 (2.3)	0.54 (0.52 to 0.57)	-1.1 (-1.1 to -1.0)	1521 (1.3)	1368 (1.2)	1.11 (1.03 to 1.20)	0.13 (0.04 to 0.22)
In-hospital death	363 (0.3)	6360 (0.7)	0.41 (0.37 to 0.45)	-0.4 (-0.5 to -0.4)	362 (0.3)	354 (0.2)	1.02 (0.88 to 1.18)	0.00 (-0.04 to 0.05)

Abbreviations: RD, risk difference; RR, risk ratio.

[a] The propensity score model included demographic information, insurance type, admission characteristics, surgery type, combined comorbidity score, comorbidities, inpatient medication use and procedures before or on postoperative day 2, hospital-level characteristics, geographic region, and calendar year.

Discussion

In this cohort study, we found that perioperative gabapentin use was associated with modestly increased risk of delirium, new antipsychotic use, and pneumonia but not with in-hospital death among adults aged 65 years or older after major surgery. Considering the increasing number of major surgeries performed in older adults[29,30] and the negative consequences of perioperative delirium, our findings raise concern about an increasingly adopted clinical practice that involves routine use of gabapentin as part of multimodal analgesia. Our study provides evidence on the safety of perioperative gabapentin use in a representative population of older patients undergoing surgery as part of routine care.

To our knowledge, more than 200 RCTs have been conducted to evaluate the effect of gabapentin on perioperative pain control, reduction in opioid use, and adverse events. The trials varied in terms of sample size (20-697 patients),[31,32] gabapentin regimen (single dose vs continued treatment with daily dose ranging from 300 mg to 1200 mg), surgery type (orthopedic, abdominal, and vascular), and study quality (low to high risk of bias). Several meta-analyses[3-5,12,13,33,34] concluded that reductions in pain intensity 24 hours after surgery and opioid-related adverse events associated with gabapentin and placebo were inconsistent and not clinically meaningful. An RCT by Hah et al[35] showed that perioperative gabapentin use had no effect on time to cessation of perioperative pain but reduced the median time to opioid cessation after surgery (25 days vs 32 days) compared with lorazepam. The rate of drug discontinuation owing to sedation or dizziness (25% in the gabapentin group and 20% in the lorazepam group) was not statistically significant, possibly because of the use of lorazepam as an active comparator. Some experts caution that the immediate harm of gabapentin may outweigh the long-term benefits of opioid cessation among older adults.[11] A recent meta-analysis[13] found higher rates of dizziness and visual disturbances after use of gabapentin, with no statistically significant associations with respiratory failure, ataxia, falls, or delirium. However, owing to the small sample size and underrepresentation of older adults in RCTs, the safety of perioperative gabapentin use in this population remains uncertain.

The main site of action of gabapentin is on the α2-δ subunit of calcium channels that are found in the peripheral and central nervous system,[36,37] which may explain its adverse effects, such as dizziness, visual disturbance, sedation, and confusion.[37] The same mechanism may also explain the increased risk of delirium, new antipsychotic use, and

Figure 2. Subgroup Analysis of the Association Between Perioperative Gabapentin Use and Delirium Diagnosis and New Antipsychotic Use

Outcome	Events, No./patients, No. (%)		RR (95% CI)	P value	RD, per 100 persons (95% CI)	P value
	Gabapentin	No gabapentin				
Delirium diagnosis						
Total population	4040/118 936 (3.4)	3148/118 936 (2.6)	1.28 (1.23 to 1.34)	NA	0.75 (0.61 to 0.89)	NA
Age, y				.02		.31
<80	2520/90 493 (2.8)	1874/90 493 (2.1)	1.34 (1.27 to 1.43)		0.71 (0.57 to 0.86)	
≥80	1528/28 468 (5.4)	1268/28 468 (4.5)	1.21 (1.12 to 1.30)		0.91 (0.56 to 1.27)	
Sex				.51		.13
Male	1692/44 407 (3.8)	1302/44 407 (2.9)	1.30 (1.21 to 1.40)		0.88 (0.64 to 1.11)	
Female	2353/74 527 (3.2)	1868/74 527 (2.5)	1.26 (1.19 to 1.34)		0.65 (0.48 to 0.82)	
Comorbidity burden				<.001		<.001
CCI <4	2491/102 174 (2.4)	2076/102 174 (2.0)	1.20 (1.13 to 1.27)		0.41 (0.28 to 0.53)	
CCI ≥4	1554/16 704 (9.3)	1109/16 704 (6.6)	1.40 (1.30 to 1.51)		2.66 (2.08 to 3.24)	
Chronic kidney disease				.08		<.001
No	2692/100 102 (2.7)	2134/100 102 (2.1)	1.26 (1.19 to 1.33)		0.56 (0.42 to 0.69)	
Yes	1353/18 787 (7.2)	982/18 787 (5.2)	1.38 (1.27 to 1.49)		1.97 (1.49 to 2.46)	
Opioid dose, MME				.48		.16
<15 mg	3601/102 855 (3.5)	2845/102 855 (2.8)	1.27 (1.21 to 1.33)		0.74 (0.58 to 0.89)	
≥15 mg	447/16 074 (2.8)	372/16 074 (2.3)	1.20 (1.05 to 1.38)		0.47 (0.12 to 0.81)	
New antipsychotic use						
Total population	944/118 936 (0.8)	805/118 936 (0.7)	1.17 (1.07 to 1.29)	NA	0.12 (0.05 to 0.19)	NA
Age, y				.89		.13
<80	572/90 493 (0.6)	460/90 493 (0.5)	1.24 (1.10 to 1.41)		0.12 (0.05 to 0.19)	
≥80	373/28 468 (1.3)	296/28 468 (1.0)	1.26 (1.08 to 1.47)		0.27 (0.09 to 0.45)	
Sex				.46		.06
Male	487/44 407 (1.1)	375/44 407 (0.8)	1.30 (1.14 to 1.48)		0.25 (0.12 to 0.38)	
Female	458/74 527 (0.6)	379/74 527 (0.5)	1.21 (1.06 to 1.38)		0.11 (0.03 to 0.18)	
Comorbidity burden				.42		.001
CCI <4	509/102 174 (0.4)	414/102 174 (0.4)	1.23 (1.08 to 1.40)		0.09 (0.03 to 0.15)	
CCI ≥4	435/16 704 (2.6)	327/16 704 (2.0)	1.33 (1.15 to 1.53)		0.65 (0.33 to 0.97)	
Chronic kidney disease				.47		.09
No	649/100 102 (0.6)	567/100 102 (0.6)	1.14 (1.02 to 1.28)		0.08 (0.01 to 0.15)	
Yes	295/18 787 (1.6)	239/18 787 (1.3)	1.23 (1.04 to 1.46)		0.30 (0.06 to 0.54)	
Opioid dose, MME				.81		.83
<15 mg	847/102 855 (0.8)	699/102 855 (0.7)	1.21 (1.10 to 1.34)		0.14 (0.07 to 0.22)	
≥15 mg	97/16 074 (0.6)	77/16 074 (0.5)	1.26 (0.93 to 1.70)		0.12 (-0.04 to 0.28)	

Propensity score matching was performed within each subgroup. The propensity score model included demographic information, insurance type, admission characteristics, surgery type, combined comorbidity score, comorbidities, inpatient medication use and procedures before or on postoperative day 2, hospital-level characteristics, geographic region, and calendar year. Combined comorbidity index (CCI) scores range from −2 to 26, with higher scores indicating greater risk of death. All *P* values are for heterogeneity. Markers indicate estimates, with horizontal lines indicating 95% CIs. MME indicates morphine milligram equivalent; D, risk difference; and RR, risk ratio.

Figure 3. Subgroup Analysis of the Association Between Perioperative Gabapentin Use and Pneumonia and In-Hospital Death

Propensity score matching was performed within each subgroup. The propensity score model included demographic information, insurance type, admission characteristics, surgery type, combined comorbidity score, comorbidities, inpatient medication use and procedures before or on postoperative day 2, hospital-level characteristics, geographic region, and calendar year. Combined comorbidity index (CCI) scores range from −2 to 26, with higher scores indicating greater risk of death. All *P* values are for heterogeneity. Markers indicate estimates, with horizontal lines indicating 95% CIs. MME indicates morphine milligram equivalent; RD, risk difference; and RR, risk ratio.

aspiration pneumonia. In addition, because gabapentin is solely metabolized through the kidneys, adverse effects may lead to more severe clinical consequences (eg, delirium and respiratory depression)[3,38,39] among older patients with a higher prevalence of multimorbidity and chronic kidney disease. It was hypothesized that gabapentin may prevent delirium by improving pain control and reducing opioid dose, whereas gabapentin-related adverse effects may increase delirium.[40] To date, several studies investigated whether gabapentin could reduce perioperative delirium. In a post hoc analysis of an RCT of 161 patients (mean age, 63 years) undergoing total knee replacement, Dighe et al[41] reported that 12.0% of patients in the gabapentin group and 9% of patients in the placebo group developed delirium (P = .53). In another RCT of 697 patients (mean age, 73 years) undergoing orthopedic surgery, Leung et al[32] showed that 24.0% in the gabapentin group and 20.8% in the placebo group had delirium (P = .30). However, the difference in the delirium incidence was not statistically significant. The RR estimates of delirium from these studies were consistent with our findings.

Limitations

Our study has limitations. The findings should be interpreted within the limitations of an administrative database study. First, delirium incidence in the present study population (3.4%) was lower compared with a previously reported incidence of 15% to 25% after major surgery[42] owing to low sensitivity (18%) and high specificity (98%) of the present study's delirium identification algorithm.[23] This delirium identification algorithm was better at identifying hyperactive delirium, which was associated with poorer prognosis compared with hypoactive or normoactive delirium.[43] For these reasons, our RD estimates may have been underestimated. Moreover, the diagnosis codes for delirium and pneumonia did not have an exact onset date in our data sets; thus, these outcomes may have been present before surgery in some patients. Second, confounding was possible. Gabapentin users were healthier and more likely to have an elective surgery compared with nonusers. After propensity score matching, the RR estimate increased from 0.84 to 1.28. If residual confounding was present in the same direction, the true RR would have been higher than the value after propensity score matching. Our sensitivity analysis suggests that unmeasured pain severity alone was unlikely to explain our results. Although the association between gabapentin and delirium did not differ by opioid dose, patients who received a higher dose had lower absolute risk of outcomes, which suggests that those patients may have been healthier than those who received a lower dose. Therefore, this subgroup analysis should be interpreted with caution. Third, outpatient medication use was unavailable in the Premier Healthcare Database. To identify patients eligible to newly receive gabapentin for perioperative pain management, we excluded those who received gabapentin before surgery, had other indications or contraindications for gabapentin, or received critical care, mechanical ventilation, or a feeding tube in the immediate perioperative period. In addition, we required at least a 2-day length of stay after surgery to define gabapentin exposure status, which may have limited the generalizability of our findings. However, the results did not change when we defined the exposure on the day of surgery without requiring a minimum length of stay after surgery.

Conclusions

In this cohort study, perioperative gabapentin use was associated with increased risk of delirium, new antipsychotic use, and pneumonia among older patients after major surgery. On the basis of these findings and those of meta-analyses of RCTs[12-14] showing a weak opioid-sparing effect of gabapentin, clinicians should reconsider routine use of gabapentin for perioperative pain management among older adults and individualize the treatment decision after assessing the risk of immediate harms vs opioid-sparing benefits of perioperative gabapentin use. For older patients who receive gabapentin as part of multimodal analgesia, daily assessment of the appropriateness of gabapentin use may be necessary to avoid unintended harm.

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Invited Commentary

Perioperative Gabapentin Use in Older Adults
Revisiting Multimodal Pain Management

Tasce Bongiovanni, MD, MPP, MHS; Timothy S. Anderson, MD, MAS; Zachary A. Marcum, PharmD, PhD

In response to the opioid crisis, surgeons nationwide have sought to decrease opioid use by adopting opioid-sparing multimodal medication regimens to treat perioperative pain.[1] For example, gabapentinoids (gabapentin and pregabalin) are now commonly administered during the perioperative period as part of "enhanced recovery after surgery" pathways, protocols designed to streamline and improve patient care after surgery. In fact, the use of gabapentinoids has tripled in the US over the past decade.[2] However, the safety of gabapentinoids in older adults has been questioned, and, according to the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults,[3] the medications are considered "potentially inappropriate" when used with opioids owing to increased risk of severe sedation-related adverse events. While multimodal pain management is promoted in perioperative care by both anesthesia and surgical societies, specific guidelines for older adults fail to address the risks or benefits of gabapentinoids.[4] In this issue of *JAMA Internal Medicine*, the work of Park et al[5] provides additional evidence of the potential harms of gabapentin use in older adults, key to understanding the overall risk-to-benefit ratio for prescribing gabapentinoids.

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Park et al[5] report the results of a retrospective cohort study using the Premier Healthcare Database, a large and robust all-payer hospital-based database, to examine in-hospital adverse clinical events associated with perioperative gabapentin use. Their retrospective cohort study identified patients 65 years or older who underwent major surgery from 2009 to 2018 and did not have gabapentin use prior to surgery. Twelve percent of the eligible cohort received perioperative gabapentin, which the authors defined as any gabapentin dose administered from postoperative day 0 through day 2. Using propensity score matching to address measured confounders, the authors found that gabapentin users had an increased risk of delirium, new in-hospital antipsychotic use, and pneumonia, but no difference in in-hospital mortality. In addition, they also found a dose-response relationship between an increased dose of gabapentin and increased risk of delirium and pneumonia.

These results are consistent with what is now a growing body of literature suggesting that gabapentin may not be the windfall medication for perioperative pain management that surgeons hoped it might be for decreasing opioid use. The adverse events reported in this study[5] (delirium, antipsychotic use, and pneumonia) add to similar findings that gabapentin, especially when used concomitantly with opioids, increases the risk of postoperative sedation and dizziness.[6] However, these results[5] should be interpreted in the context of study strengths and limitations. Because it was an observational study, the reader must consider measured and unmeasured confounders. Park et al used a robust set of patient- and hospital-level characteristics to reduce measured confounding via propensity score matching, but the investigators lacked data on prehospitalization medication use and postdischarge outcomes. In addition, the authors performed a sensitivity analysis to address the most likely unmeasured confounder for the association between gabapentin and delirium—pain severity—showing that unmeasured severe pain was unlikely to fully explain away the findings. This type of sensitivity analysis is exemplary for generating clinical evidence using observational data.

On the other hand, it is not clear why gabapentin use was associated with an increased risk of delirium and pneumonia but not in-hospital mortality.[5] One possible explanation is that in-hospital mortality was a relatively rare outcome, and the risk difference results for delirium and pneumonia, while statistically significant, were small on an absolute scale. This may have limited the ability to detect a difference for a composite outcome such as mortality. Moreover, although the study includes almost 1 million patients, more than three-quarters of included patients had undergone orthopedic surgeries. Therefore, the study results mostly apply to older adults undergoing orthopedic surgeries. A sensitivity analysis was not reported among patients by type of surgery, so it is unclear whether surgery type might influence the overall results.

With these study strengths and limitations in mind, how do the results from Park et al[5] fit into the overall clinical landscape of perioperative pain management for older adults? Undertreatment of pain has garnered national attention as an indicator of poor surgical quality. Furthermore, the ability to participate in and successfully complete rehabilitation and return to the community can be hampered by inadequate pain control.[7] However, the current approaches for postoperative