Perioperative Gabapentin Does Not Reduce Postoperative Delirium in Older Surgical Patients

A Randomized Clinical Trial

Jacqueline M. Leung, M.D., M.P.H., Laura P. Sands, Ph.D., Ningning Chen, Ph.D., Christopher Ames, M.D., Sigurd Berven, M.D., Kevin Bozic, M.D., Shane Burch, M.D., Dean Chou, M.D., Kenneth Covinsky, M.D., Vedat Deviren, M.D., Sakura Kinjo, M.D., Joel H. Kramer, Psy.D., Michael Ries, M.D., Bobby Tay, M.D., Thomas Vail, M.D., Philip Weinstein, M.D., and the Perioperative Medicine Research Group*

ABSTRACT

Background: Postoperative pain and opioid use are associated with postoperative delirium. We designed a single-center, randomized, placebo-controlled, parallel-arm, double-blinded trial to determine whether perioperative administration of gabapentin reduced postoperative delirium after noncardiac surgery.

Methods: Patients were randomly assigned to receive placebo (N = 347) or gabapentin 900 mg (N = 350) administered preoperatively and for the first 3 postoperative days. The primary outcome was postoperative delirium as measured by the Confusion Assessment Method. Secondary outcomes were postoperative pain, opioid use, and length of hospital stay.

Results: Data for 697 patients were included, with a mean ± SD age of 72 ± 6 yr. The overall incidence of postoperative delirium in any of the first 3 days was 22.4% (24.0% in the gabapentin and 20.8% in the placebo groups; the difference was 3.20%; 95% CI, 3.22% to 9.72%; $P = 0.30$). The incidence of delirium did not differ between the two groups when stratified by surgery type, anesthesia type, or preoperative risk status. Gabapentin was shown to be opioid sparing, with lower doses for the intervention group *versus* the control group. For example, the morphine equivalents for the gabapentin-treated group, median 6.7 mg (25th, 75th quartiles: 1.3, 20.0 mg), *versus* control group, median 6.7 mg (25th, 75th quartiles: 2.7, 24.8 mg), differed on the first postoperative day ($P = 0.04$).

Conclusions: Although postoperative opioid use was reduced, perioperative administration of gabapentin did not result in a reduction of postoperative delirium or hospital length of stay. (**ANESTHESIOLOGY** 2017; 127:633-44)

DELIRIUM is a major challenge facing geriatric practice due to its prevalence, complex etiology, and potentially severe impact on patients and their families. One setting in which high rates of delirium are found is after major surgery. Postoperative delirium is associated with longer hospital stays, poor functional outcomes, and higher healthcare costs.[1] Despite the prevalence and clinical importance of postoperative delirium, an effective therapy to prevent its occurrence has not been identified.

Patient risk for the development of delirium is determined by predisposing baseline vulnerabilities and exposure to factors that precipitate poor patient outcomes (*e.g.*, pain or new medications associated with surgery). We and others have identified pain after surgery as an independent predictor of postoperative delirium[2] and therefore a potentially important and modifiable precipitating factor for adverse cognitive outcomes. Opioids are another potential risk factor, because patients with postoperative delirium also received

What We Already Know about This Topic

- Pain perception is a major risk factor for the development of postoperative delirium after major surgery. Patients who develop delirium often receive more opioids.
- In patients undergoing major surgery, the adjunctive administration of gabapentin was evaluated for its efficacy in reducing pain, opioid use, and delirium.

What This Article Tells Us That Is New

- Preoperative and postoperative administration of gabapentin reduced postoperative opioid use.
- However, gabapentin did not reduce the incidence of delirium after major surgery.

more intravenous opioids postoperatively than those without delirium.[2]

Based on results from a pilot study, we found a promising intervention involving the use of an adjunctive nonopioid

---

This article is featured in "This Month in Anesthesiology," page 1A. This article has an audio podcast.

*Members of the Perioperative Medicine Research Group are listed in appendix 1.

therapy to reduce postoperative pain and the consumption of opioids, which ultimately resulted in a reduction of the incidence of postoperative delirium.[3] Our main objective was to test the hypothesis that rates of delirium could be reduced through intensive supplementary pain management in addition to standard opioid analgesics after surgery. We conducted a double-blind, placebo-controlled study using gabapentin as an additional agent in the treatment of postoperative pain in older patients undergoing major noncardiac surgery.

Our specific aims were as follows: (1) to assess whether the administration of gabapentin was associated with a decreased occurrence of delirium; (2) to determine the extent to which gabapentin-associated reductions in pain and/or opiate use reduced the occurrence of delirium; and (3) to determine whether the administration of gabapentin was associated with shorter hospital stays. We hypothesized that postoperative intensive pain management using an adjuvant agent, gabapentin, would lead to a decrease in the amount of opioids received and a decrease in postoperative pain experienced, thereby resulting in a decrease in the incidence of postoperative delirium.

Materials and Methods

Study Design
This was a double-blind, randomized, placebo-controlled study of 750 patients 65 yr of age or older undergoing spine surgery or joint replacement surgery at the University of California San Francisco Medical Center (San Francisco, California). The study received approval from the institutional review board, and all of the patients provided written informed consent. The trial was registered with clinicaltrials.gov (updated in April 2017 to clarify primary outcome; Identifier NCT00221338) and conducted in accordance with the original protocol. We formed a data and safety monitoring board to monitor participant safety and data quality and to evaluate the progress of the study (appendix 2).

Participants
Potential subjects were recruited within 1 week before the planned surgical procedure. The inclusion criteria included patients 65 yr of age or older who were undergoing surgery involving the spine or arthroplasty of hips or knees who were fluent in English and with an anticipated length of hospital stay of at least 3 days after surgery. These types of patients were selected because they have substantial preoperative and postoperative pain and had a high incidence of postoperative delirium.[2]

Exclusion criteria included patients with known sensitivity to gabapentin; use of preoperative gabapentin, pregabalin, or other antiepileptics, spinal surgery that was two staged involving more than one surgical procedure to be performed within the same hospitalization period; emergency surgery;

preoperative renal dialysis; or opioid tolerance (total daily dose of an opioid at or more than 30 mg morphine equivalent for more than 1 month within the past year; source: Institutional Chronic Pain Management Center).

Randomization
A simple randomization method was used for this trial. Randomization into placebo or the gabapentin groups was created by a computerized random number generation method by the study statistician using a 1:1 randomization ratio. Randomization occurred after consent for study participation was obtained during the preoperative interview.

Blinding
The randomization schedule was blinded from the investigators and treating clinicians because it was kept and administered by the central research pharmacy. The assignment of gabapentin *versus* placebo was made on the day of surgery, and the study drug was delivered by the research pharmacists directly to the preoperative holding area to be administered by clinical nurses to the study patients.

Clinical Management
A balanced anesthetic was administered for study patients who underwent spinal surgery, which included a volatile anesthetic agent and intravenous agents such as propofol and fentanyl. Preoperatively, a femoral nerve block was placed for patients undergoing knee arthroplasty, and a lumber plexus block was placed for patients undergoing hip arthroplasty. Ropivacaine was used for both blocks. In addition to the blocks, the patients undergoing arthroplasty typically received either spinal anesthesia or general anesthesia. Postoperatively, all of the patients who had undergone spine surgery received on-demand patient-controlled analgesia with intravenous hydromorphone. For patients who underwent arthroplasty, postoperative analgesia was administered *via* the femoral nerve block or the lumbar plexus block for the first 2 postoperative days. In the case of additional analgesia for patients with incomplete analgesia from regional analgesia (less than 10% of cases), typically intravenous hydromorphone was administered *via* patient-controlled analgesia, and oral hydrocodone/acetaminophen, oxycodone/acetaminophen, or oxycodone was administered on demand by nurse administration.

Gabapentin Dosing Regimen
We administered either gabapentin 900 mg (or placebo) orally 1 to 2 h before surgery and anesthesia. This dose continued postoperatively for the first 3 days (300 mg three times per day). We adjusted the dose of gabapentin based on patient preoperative and postoperative renal function, as described previously.[4] The rationale for choosing a clinical dose of 900 mg was based on a previous study, which demonstrated that this dose was well tolerated by older patients

with herpes zoster and was effective in reducing the median pain level from baseline by more than 50%.[5] Larger doses used in previous studies targeted primarily relatively healthy and younger surgical patients.[6–15]

Measurement of Cognitive Status

Trained research assistants who were blinded to the study drug assignment conducted cognitive tests preoperatively to determine the presence of delirium and to determine baseline cognitive function. The cognitive testing occurred in the preoperative clinic or ward and was repeated again daily for 3 days after surgery. Preoperative cognitive status was measured by the Telephone Interview for Cognitive Status (TICS) test,[16] which was adapted from the Mini-Mental State Examination for use either in person or over the telephone. To minimize patient test burden, we used the nine-item word list test in lieu of the word naming in the TICS test during the preoperative testing.[1] (The following cognitive tests were administered: the Word List Learning, the Digit Symbol Test, and the Controlled Verbal Fluency Test. Results are not included in this article.)

Endpoints

The primary outcome was postoperative delirium as measured by the Confusion Assessment Method (CAM). Secondary outcomes included postoperative pain, opioid use, and the length of hospital stay.

Measurement of the Primary Outcome: Postoperative Delirium

For the occurrence of delirium, we used the CAM rating scale,[17] which was developed as a screening instrument based on operationalization of Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Text Revision, criteria for use by nonpsychiatric clinicians in high-risk settings. CAM has a sensitivity of 94% to 100%, a specificity of 90% to 95%, a high interobserver reliability,[17] and a convergent agreement with four other cognitive status tests. Identifying delirium requires the presence of acute onset and fluctuating course, inattention, and either disorganized thinking and/or altered level of consciousness as measured by the CAM rating scale. Training of the research assistants in the use of the CAM was described in our previous publication.[17]

At approximately 24 h after surgery, the patient was rated on the Richmond Agitation and Sedation Scale (RASS).[18] If a patient was too sedated to be interviewed (RASS score of −4 or −5), delirium status would be considered unevaluable. The severity of delirium was measured using the Memorial Delirium Assessment Scale (MDAS),[19] an instrument that contains 10 items using information from the Mini-Mental State Examination and structured interview to rate delirium severity.

Measurement of Secondary Outcomes

During each assessment of cognitive status and delirium, patients rated their pain using the 11-point verbal version of the visual analog scale (0 = no pain and 10 = the worst pain imaginable). Postoperative intravenous opioid use was measured for the first 3 postoperative days. We converted all opioids to morphine equivalents as follows: hydromorphone and fentanyl doses were converted to morphine equivalents using the conversion formula: 1.5 mg hydromorphone = 10.0 mg morphine equivalents, 0.1 mg fentanyl = 10 mg morphine equivalents.[20–22] Detailed conversion for all opioids are shown in appendix 3. Postoperative length of stay was measured and compared between interventional and control groups.

Measurement of Other Covariates

Preoperative risk was measured using the American Society of Anesthesiologists physical classification[23] and the Charlson comorbidity index.[24] Mood was measured using the standard screening tool for geriatric depression, the 15-question Geriatric Depression Scale.[25] Other covariates included functional status including Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL). Independence in ADL and IADL was determined by asking the subjects if they needed the help of another person to do the activity.

Subgroup Analyses

For subgroup analysis, which was preplanned, we stratified patients by preoperative risk status: low risk was defined as patients with risk scores of three or less and high risk with risk score of more than 3 based on our previous risk prediction index where one point was assigned each to female sex, history of central nervous system disorder, high surgical risk, and age greater than 75 yr. A TICS score between 30 to 35 was assigned one point, and a TICS score less than 30 was assigned two points.[26]

We controlled for the severity of the surgical procedures such as duration and blood loss statistically (see statistical analysis section for details). Briefly, surgical risk was estimated by taking into consideration the type and duration of surgery and intraoperative blood loss.[27]

Measurement of In-hospital Drug-related Side Effects and Complications

In addition to the primary and secondary outcomes in the study, we also measured the frequency of other potential drug-related side effects and the occurrence of other nonfatal postoperative adverse outcomes (appendix 4) using predefined criteria developed by our previous studies.[28,29]

Sample Size Calculation

The sample size was calculated based on the ability to detect a significant difference in rates of delirium between interventional *versus* placebo groups with an absolute difference in the delirium rate of 10% (25% *vs.* 15%) with 90% power. The level of significance was set at two-sided $\alpha = 0.05$ to support the hypothesis that the delirium rates in the gabapentin

group were different than that in the placebo group. The rates of delirium described above were determined using a combination of our earlier published pilot data of gabapentin delirium[3] and rates of delirium among more than 500 subjects enrolled in our prospective observational study.[2]

Statistical Analysis

All of the primary and secondary outcomes were analyzed according to the intention-to-treat paradigm. For the primary outcomes, to compare the postoperative delirium rates between gabapentin and placebo groups, we performed a chi-square test to determine the association between gabapentin administration and delirium rate. For the secondary outcomes, subjectively reported pain scores by the visual analog scale were stratified into low (1 to 3), medium (4 to 6), or high (7 to 10) for each postoperative day. The difference in pain levels was measured by chi-square between gabapentin and placebo groups. Opioid use was defined as low *versus* high. Cutoff value for opioid dose use was based on the top third quartile (75th percentile) on 3 postoperative days, respectively. Specifically, a daily use of more than 22 mg of morphine equivalents in a 24-h period was considered to be the top 75th percentile of opioid doses, a high dose. Low opioid use was defined as patients who used 22 mg or less of morphine equivalents in a 24-h period. The

justification of stratifying opioids dose into high- *versus* low-dose for analysis was based on our previous work on a model of prediction of postoperative delirium.[26] The difference in morphine equivalent dosing on postoperative day 1 between the gabapentin and placebo groups was determined by the Mann–Whitney U test. Hospital lengths of stay between groups were compared using the unpaired *t* test.

In subgroup analyses, we conducted poststudy stratification of clinical characteristics relevant to translation of results. Postoperative delirium rates were stratified by surgery type, anesthesia type, dose of postoperative opiates and pain, and preoperative risk, and reported *P* values were adjusted using Bonferroni correction as needed.

In addition, logistic regression was performed to analyze the effect of gabapentin on postoperative delirium with sex and ADL as covariates. For other outcome variables of interest, including the MDAS, *P* values were calculated based on the chi-square test if the variables were categorical; otherwise *P* values were based on independent t tests or Mann–Whitney U test for data that were not normally distributed. To compare delirium-free days between the two treatment groups, we performed the Mantel–Haenszel test to take into account the ordinal distribution of delirium-free days. All of the data were reported as mean ± SD. Median values (25th, 75th quartiles) were included if the data were not normally distributed.
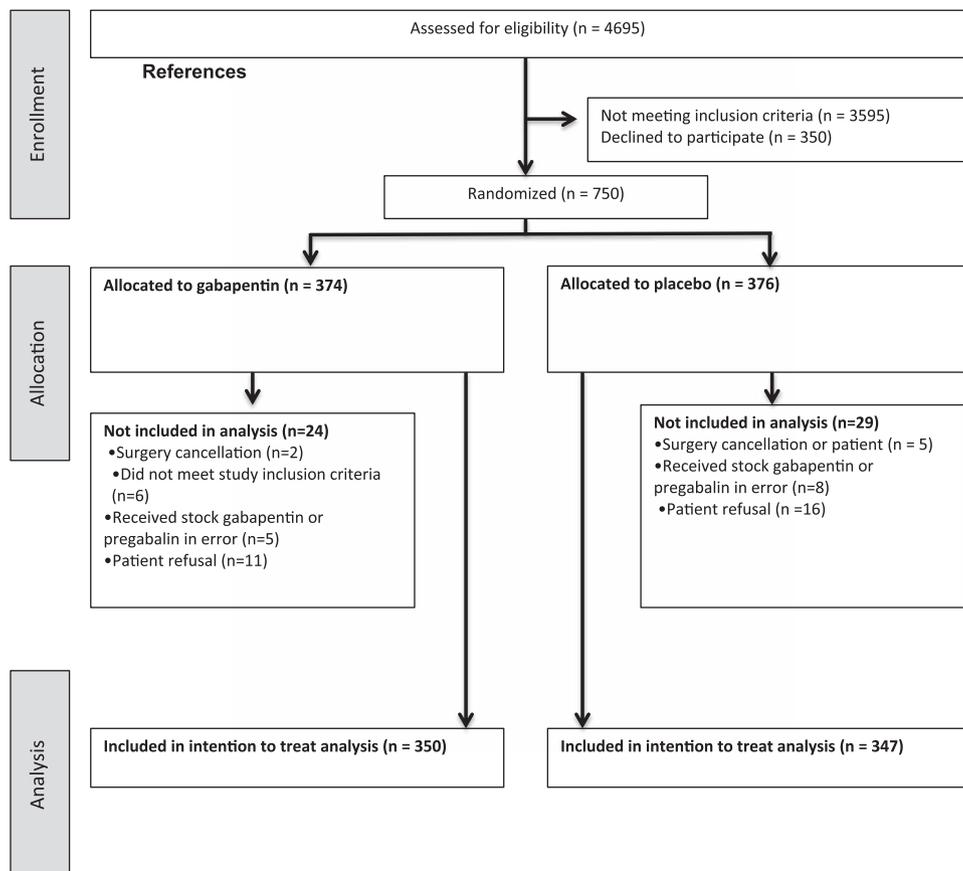
Fig. 1. The CONSORT (Consolidated Standards of Reporting Trials) diagram depicting patient recruitment scheme is shown.

Results

Patient Recruitment

The study began in January 2006 and ended in January 2014. The patient recruitment scheme is depicted in figure 1. Overall, 697 patients were included in this intention-to-treat algorithm. A total of 198 patients had total hip arthroplasty, 183 had knee arthroplasty, and 316 underwent spine surgery. The demographic variables of the patients who received gabapentin *versus* placebo are shown in table 1. Overall, there were more women (55.1% *vs.* 45.5%) and more patients who were dependent in one or more activities of daily living (34.4% *vs.* 25.7%) in the gabapentin compared with the placebo group.

Completion of Study Drugs

The compliance of study drugs received by patients was similar between the gabapentin- *versus* the placebo-treated patients. All of the patients received the preoperative study drugs. For the first postoperative day, 88.6% of patients in the gabapentin-treated group completed the assigned dosing *versus* 92.8% of the patients who received placebo; for the second postoperative day, 80.9% of patients in the gabapentin completed the assigned dosing *versus* 80.6% in the placebo group; and for the third postoperative day, 43.1%

of patients in the gabapentin completed the assigned dosing *versus* 39.6% in the placebo group. The lower rate of receiving study drugs on the third postoperative day was in part due to earlier unanticipated discharge (84% of patients who did not receive the study drug or placebo were discharged earlier than anticipated).

Study Outcomes Measurement: Primary and Secondary Outcomes

No patient had preoperative delirium. The overall incidence of postoperative delirium in any of the first 3 days for the entire cohort was 22.4% (95% CI, 19.3% to 25.5%; 24.0% in the gabapentin group; 95% CI 19.2% to 28.8%; and 20.8% in the placebo group; 95% CI 16.2% to 25.4%). The difference of 3.2% (95% CI, −3.2% to 9.7%) was not statistically significant ($P = 0.30$). When stratifying by surgery type (table 2) or anesthesia type (table 3), the incidence of postoperative delirium was also not significantly different between the gabapentin *versus* the placebo group.

Pain scores for the first 3 postoperative days are shown in table 4. Overall, patients who experienced high postoperative pain levels had higher rates of postoperative delirium compared with those with lower pain levels (19.5%; 95% CI, 14.9% to 24.1%; *vs* 9.1%; 95% CI 6.3% to 11.9%; $P = 0.0001$). However, the delirium rates were not significantly

Table 1. Comparisons between Drug Assignment Groups: Surgical/Anesthetic Factors

Variable	Gabapentin (N = 350)	Placebo (N = 347)	P Value
Age, mean ± SD, y	73±6	73±6	0.10
Sex, women	193 (55.1%)	158 (45.5%)	0.01
Race, white	323 (92.3%)	315 (90.8%)	0.33
Ethnicity, Hispanic	10 (2.9%)	11 (3.2%)	0.81
Education, college or higher	218 (62.3%)	217 (62.5%)	0.95
Alcohol use, 2 or more drinks per day	25 (7.1%)	31 (8.9%)	0.38
At least 1 of 5 ADLs	43 (12.3%)	25 (7.2%)	0.03
At least 1 of 7 IADLs	206 (58.9%)	194 (55.9%)	0.45
Preoperative GDS, ≥ 6	50 (14.3%)	42 (12.1%)	0.41
Preoperative TICS score, mean ± SD	34.5±3.5	34.5±3.1	0.89
History of CNS disorder, yes	208 (59.4%)	213 (61.4%)	0.65
Charleston comorbidity index, mean ± SD	0.5 ± 0.9	0.6 ± 1.0	0.43
ASA III/IV	119 (34%)	128 (36.9%)	0.43
Surgical risk II	336 (96.0%)	334 (96.3%)	0.86
Surgical risk III	14 (4.0%)	13 (3.7%)	

ADL = activities of daily living; ASA = American Society of Anesthesiologists physical classification; CNS = central nervous system; GDS = geriatric depression score; IADL = instrumental activities of daily living; TICS = Telephone Interview for Cognitive Status.

Table 2. Association between Drug Assignment and Delirium by Surgery Type with All ITT Patients

	Hip P Value (N = 198)			Knee P Value (N = 183)			Spine P Value (N = 316)		
	Gabapentin	Placebo		Gabapentin	Placebo		Gabapentin	Placebo	
Delirium on any of the first 3 postoperative days, n/N (%)	19/101 (18.8)	9/97 (9.3)	0.09 (0.27)*	27/94 (28.7)	17/89 (19.1)	0.18 (0.54)*	38/155 (24.5)	46/161 (28.6)	0.49 (1.00)*
Mean difference (95% CI), %	9.5 (−1.0 to 20.1)			9.6 (−3.7 to 22.9)			4.1 (−14.4 to 6.3)		

*P values were adjusted by Bonferroni correction.
ITT = intention to treat.

Table 3. Incident Postoperative Delirium by Drug Assignment and Anesthetic Type

Delirium on Any of the First 3 Postoperative Days	Gabapentin (N = 350)	Placebo (N = 347)	Chi-square Test: *P* Value
Group 1, n/N (%)	42/145 (30.0)	49/152 (32.2)	0.63 (0.63)*
Mean difference (95% CI), %		−2.2 (−14.4 to 7.9)	
Group 2, n/N (%)	6/23 (26.1)	0/23 (0.0)	0.03 (0.09)*
Mean difference (95% CI), %		26.1 (4.0 to 48.4)	
Group 3, n/N (%)	36/132 (27.3)	23/120 (19.2)	0.17 (0.34)*
Mean difference (95% CI), %		8.1 (−3.0 to 19.3)	

Group 1 = general anesthesia only; group 2 = general plus regional anesthesia; group 3 = regional anesthesia only.

*P values were adjusted by Bonferroni correction.

Table 4. Postoperative Pain Scores Stratified by Treatment Groups

	Gabapentin	Placebo
Postoperative day 1	4 ± 3 (3)	4 ± 3 (4)
	n = 343	n = 343
Postoperative day 2	3 ± 3 (2)	4 ± 3 (3)
	n = 335	n = 343
Postoperative day 3	3 ± 3 (3)	3 ± 3 (3)
	n = 299	n = 291

The postoperative pain scores (visual analog scores) are shown as mean ± SD and median (in parentheses) for the first 3 postoperative days for the two treatment groups. No significant difference was found between the mean pain scores in the gabapentin *versus* the placebo groups.

Table 5. Delirium Rate by Pain and Morphine Equivalent Dosing on the First Postoperative Day Stratified by Treatment

Treatment, Pain and Opioid	Gabapentin, n/N (%)	Placebo, n/N (%)
Low and low	15/158 (9.5)	10/127 (7.9)
Medium and low	10/84 (11.9)	17/108 (15.7)
High and low	17/60 (28.3)	9/63 (14.3)
Low and high	1/11 (9.1)	0/14 (0)
Medium and high	0/9 (0)	2/14 (14.3)
High and high	6/10 (60.0)	3/11 (27.3)

Morphine equivalence dosing was defined as low *versus* high. The cutoff value for low dose use was based on the 75th percentile on 3 postoperative days, respectively. Specifically, a daily use of more than 22 mg morphine in a 24-h period was considered to be the top 75% of opioid doses, high dose. Low opioid uses were defined as patients who used 22 mg or less morphine in a 24-h period. Subjectively reported pain scores by the visual analog scale were stratified into low (0 to 3), medium (4 to 6), or high (7 to 10). The overall difference in distributions between the two groups was not significant (by Wald test statistic = 2.89; *P* = 0.09).

different between the gabapentin and placebo groups when stratified by pain levels: delirium in low pain level group was 9.2% (95% CI, 5.5% to 14.8% gabapentin) *versus* 6.9% (95% CI, 3.5% to 12.7% placebo; *P* = 0.16); in the medium pain level group it was 11.6% (95% CI, 6.2% to 20.2% gabapentin) *versus* 15.6% (95% CI, 9.8% to 23.5% placebo; *P* = 0.52); and in the high pain level group it was 33.4% (95% CI, 22.0% to 44.6% gabapentin) *versus* 17.1% (95% CI, 9.7% to 27.8% placebo; *P* = 0.05). Data for postoperative days 2 and 3 were similar (table 5).

Despite the lack of effect on postoperative delirium, gabapentin was shown to be opioid sparing, particularly in the first postoperative day. For example, morphine equivalents are lower for the gabapentin-treated group, with a median (25th, 75th quartile) of 6.7 mg (1.3, 20.0 mg) when compared with the control group of 6.7 mg (2.7, 24.8 mg) for the first postoperative day (*P* = 0.04 based on the Mann–Whitney U test). Note that this test compares the rank sum between the two groups. Boxplots of the opioid use for the first 3 days are shown in figure 2. The amount of postoperative opioid use and pain level were not associated with postoperative delirium (table 5).

When we stratified patients with respect to their preoperative risk of developing postoperative delirium, high-risk patients had significantly higher rates of postoperative delirium than low-risk patients. However, the rates of delirium on any of the postoperative days were not significantly different between the gabapentin and placebo groups with preoperative risk stratification. The incidence of postoperative delirium in any of the first 3 postoperative days was 21% in the

low-risk gabapentin group *versus* 18.8% in the low-risk placebo group (*P* = 0.56) and 47.5% in the high-risk gabapentin group *versus* 39.4% in the high-risk placebo group (*P* = 0.65).

We also compared the severity of delirium using the MDAS. Again, comparison of the MDAS scores between the gabapentin- and placebo-treated groups was not different for each of the 3 postoperative days (day 1, 5.2 ± 2.8 *vs.* 5.2 ± 2.5, *P* = 0.85; day 2, 4.6 ± 2.7 *vs.* 4.9 ± 2.8, *P* = 0.35; day 3, 3.8 ± 2.4 *vs.* 4.1 ± 2.1, *P* = 0.37).

All of the study patients had delirium data for 1 or more of the first 3 postoperative days. For those with missing delirium data for 1 or 2 of the 3 postoperative days (n = 102), we determined whether missing data might bias the results. Overall, patients with missing delirium data compared with those with no missing data were younger, more likely to be men, had higher level of education, a higher incidence of alcohol use, a lower incidence of a history of central nervous system disorders, were less likely to depend on one or more activities of IADL, and had lower mean Charlson comorbidity scores. Excluding the 102 patients with incomplete delirium assessments, the rates of delirium between gabapentin and placebo groups were 28.0% *versus* 24.4% (95% CI of the difference, −3.8% to 11.0%; *P* = 0.67). This comparison suggests that those patients with missing delirium data did not have covariates that were associated with an increased risk of postoperative delirium.
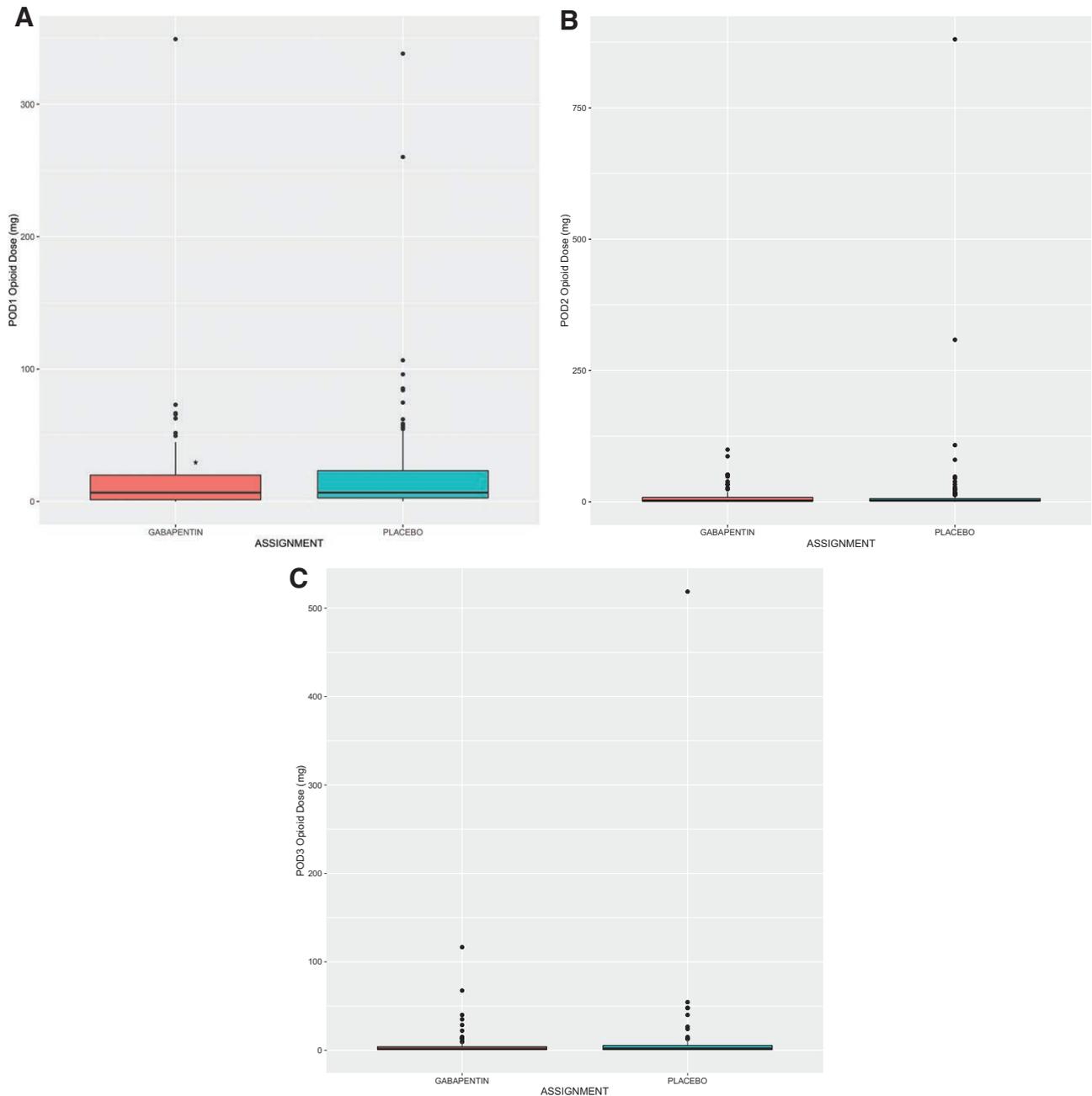
Fig. 2. (*A*) Boxplots of opioid use (in morphine equivalents) for the first postoperative day (POD) is shown. The gabapentin and placebo groups are shown on the *x-axis*. On the *y-axis* is shown the morphine equivalents (in milligrams). A typical *box plot* showed the median (*thicker black line in the middle of the box*) and first and third quartiles represented by the *bottom and top of the box*, respectively. The median (25th, 75th quartile) of morphine equivalents for the gabapentin-treated group 6.7 mg (1.3, 20.0 mg) *versus* the control group 6.7 mg (2.7, 24.8) differed on the first postoperative day ($P = 0.04$). The *asterisk* indicates significant difference between the gabapentin *versus* placebo groups based on Mann–Whitney U test. See text for details. (*B*) Boxplots of opioid use (in morphine equivalents) for the second postoperative day (POD). The median morphine equivalent dose in the gabapentin group was 1.0 (2.3 to 8.4 mg) *versus* 1.0 (2.7 to 6.0 mg) in the placebo group ($P = 0.48$). (*C*) Boxplots of opioid use (in morphine equivalents) for the third postoperative day (POD). The median morphine equivalent dose in the gabapentin group was 0.7 (1.7 to 4.0 mg) *versus* 0.7 (2.0 to 5.3 mg) in the placebo group ($P = 0.72$).

We additionally evaluated whether patients who were treated with gabapentin had a difference in delirium-free days for the first 3 postoperative days when compared with placebo-treated patients. This analysis included all of the intention-to-treat patients with a hospital length of stay of 3 days or longer, and patients with missing delirium data were excluded. Again, the comparison did not show any difference between the two groups (table 6).

Table 6. Delirium-free Days for Postoperative Days 1 to 3 Between Gabapentin and Placebo Groups

Delirium-free Days	Gabapentin (N = 295), n (%)	Placebo (N = 293), n (%)	Mantel–Haenszel Test: P Value
0	6 (2.0)	7 (2.4)	0.63
1	20 (6.8)	17 (5.8)	
2	53 (18.0)	47 (16.0)	
3	216 (73.2)	222 (75.8)	

Data include all intention-to-treat patients with the length of hospital stay of 3 or more days (patients with missing delirium data were excluded).

Regarding the secondary outcome, the length of hospital stay in patients with postoperative delirium was significantly longer than those without delirium (5.5 ± 3.1 days, 95% CI, 5.2 to 5.8 days *vs.* 3.9 ± 2.8 days, 95% CI, 3.6 to 4.2 days; $P < 0.0001$). However, there was no difference in length of hospital stay between patients treated with gabapentin *versus* placebo (4.4 ± 3.4 days, 95% CI, 4.0 to 4.7 days *vs.* 4.1 ± 2.3 days, 95% CI, 3.9 to 4.3 days; $P = 0.26$).

Safety Evaluation of Gabapentin Administration

Regarding the safety of perioperative gabapentin administration, we measured postoperative clinically significant oversedation as determined by the RASS scores and also postoperative adverse events. Overall, the incidence of serious oversedation rates (RASS scores of –4 or –5) were not different on any of the postoperative days between the gabapentin or placebo groups (day 1, 2/333 = 0.6% *vs.* 1/329 = 0.3%, $P = 0.61$; day 2, 4/321 = 1.3% *vs.* 1/328 = 0.3%, $P = 0.37$; and day 3, 0/289 = 0% *vs.* 1/284 = 0.4%, $P = 0.60$). Detailed comparison of the RASS scores is shown in table 7. We also compared other potential drug-related side effect, such as dizziness, and no significant difference was found between study groups, including 10 of 345 patients (2.9%) in the gabapentin group *versus* 5 of 340 patients (1.5%) in the placebo group ($P = 0.30$). No patient reported nystagmus or ataxia in either study group. The incidence of adverse postoperative events relating to the cardiovascular,

pulmonary, renal, or neurologic systems and infection and thrombotic events also was not significantly different between gabapentin- *versus* placebo-treated groups (8.9% *vs.* 12.7%; $P = 0.13$).

Discussion

This large prospectively conducted randomized clinical trial revealed no difference in rates of postoperative delirium when gabapentin was administered perioperatively to older surgical patients when compared with placebo, despite its opioid-sparing effects.

Comparison with Previous Studies

Aside from our previous pilot study,[30] no previous study has investigated the use of perioperative gabapentin as a means to reduce postoperative delirium. However, there have been a number of other pharmacologic interventional trials aimed at delirium reduction in surgical patients but with mixed results. Most studies found no effects of pharmacologic treatments with antipsychotics or anticholinesterase agents on delirium reduction.[31–33] Although several small studies have suggested that antipsychotics may reduce the risk of delirium, these finding were not supported by meta-analyses.[34,35] Moreover, the prophylactic administration of both conventional and atypical antipsychotics to older patients is potentially hazardous, with cardiac and metabolic side effects reported because of age-related changes in pharmacokinetics and pharmacodynamics, as well as potential adverse drug interactions with other medications.[36] Hence, the evidence to date does not support the use of antipsychotics for prevention of postoperative delirium.

Other types of intervention reported involved the evaluation of sedatives or anesthetic agents, such as dexmedetomidine or ketamine.[37,38] However, these clinical trials produced mixed results, and definitive therapies based on trials with adequate sample size have yet to be developed. A recent large trial in postoperative patients recovering in the intensive care unit reported that intravenous infusion of dexmedetomidine

Table 7. Bivariate Association between Drug Assignments and Postoperative Sedation Scores

Variable (N = 697)	Gabapentin (N = 350), n/N (%)	Placebo (N = 347)	P Value
Sedation on POD 1, normal (≥ 0)	238/333 (71.5)	229/329 (69.6)	0.61
Median (–1 to –3)	93/333 (27.9)	99/329 (30.1)	
Serious (–4 and –5)	2/333 (0.6)	1/329 (0.3)	
Sedation on POD 2, normal (≥ 0)	247/321 (76.9)	251/328 (76.5)	0.37
Median (–1 to –3)	70/321 (21.8)	76/328 (23.2)	
Serious (–4 and –5)	4/321 (1.2)	1/328 (0.3)	
Sedation on POD 3, normal (≥ 0)	233/289 (80.6)	229/284 (80.6)	0.60
Median (–1 to –3)	56/289 (19.4)	54/284 (19.0)	
Serious (–4 and –5)	0/289 (0)	1/284 (0.4)	

In this table, the sedation scores were reported for 3 postoperative days. The P value reflects comparison of the range of sedation scores for each specific postoperative day between study groups.
POD = postoperative day.

immediately after surgery reduced the occurrence of postoperative delirium when compared with placebo.[39] Whether these results can be generalized to nonintensive care unit patients remains to be determined. In contrast to pharmacologic prophylactic treatment, nonpharmacologic intervention, such as fast-track surgery,[40] specialized postoperative geriatric wards,[41] and proactive geriatric consultation,[42] reported more success in delirium reduction. Thus, a recent systematic assessment conducted by the American Geriatrics Society concluded that only nonpharmacologic interventions were proven to be efficacious and should be widely practiced. Recently, it has been proposed that deep anesthetic depth contributes to an increased rate of postoperative delirium.[43–46] However, the mechanism of this deep anesthesia effect has not been completely elucidated despite a recent report that burst suppression on electroencephalogram indicative of deep anesthesia may have been the etiologic factor.[46]

Our results did not support the second hypothesis that gabapentin-associated reductions in pain and/or opiate use reduced the occurrence of delirium. Although we did find that gabapentin was opioid sparing, we did not demonstrate that the opioid-sparing effect resulted in a reduction of postoperative delirium. It is likely that the opioid-reducing effect of gabapentin was attenuated by the concomitant use of postoperative analgesia, such as femoral nerve block or lumbar plexus block in some of our patients who underwent arthroplasty. This explanation is in part supported by previous studies, which demonstrated that reducing opioid exposure may be achieved with regional analgesia, such as femoral nerve block or fascia iliaca block[47,48]; both of these techniques have been shown to be associated with lower risk of postoperative delirium, but definitive large-scale trials are lacking.

A recent meta-analysis examined the effect of preoperative gabapentin in reducing postoperative opioid consumption.[49] In the 17 randomized trials that were examined, the dosages of gabapentin ranged from 300 to 1,200 mg. Our study chose the 900-mg preoperative dose, which is within the range identified in this review. Of note, meta-regression analyses identified a statistical association between reduced postoperative opioid consumption and gabapentin dosage.[49]

Potential Study Limitations

First, despite a computerized randomization of recruited patients, we observed some unbalance across treatment groups with respect to preoperative patient characteristics. However, inclusion of the covariates that were different between groups did not affect results of the outcome measurements. Second, we studied patients with three types of surgery, and the methods of intraoperative anesthetics and postoperative management were different between groups. However, inclusion of the type of surgery and anesthetics as covariates did not affect the rates of postoperative delirium between

the gabapentin-treated and placebo groups. Third, because of changing perioperative practice patterns during the duration of the study, the inclusion of multimodal oral analgesics, such as acetaminophen and nonsteroidal anti-inflammatory agents administered to the placebo patients who underwent arthroplasty surgery perioperatively might have resulted in lower rates of postoperative delirium in that group when compared with historical control subjects. Lastly, we did not specifically measure other opioid-related side effects, such as pruritus, nausea, vomiting, and whether gabapentin through its opioid-sparing action produced salutary effects will need to be determined by additional investigations.

Summary

Results from this large, randomized, double-blind, placebo-controlled trial showed that perioperative administration of gabapentin did not result in a lower rate of postoperative delirium in older patients undergoing major spine and arthroplasty surgery, despite its opioid-sparing effects. Our results suggest that the prophylactic use of gabapentin as a means to reduce postoperative delirium is not indicated.

Research Support

Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: Jacqueline.Leung@ucsf.edu. Raw data available at: Jacqueline.Leung@ucsf.edu.

Correspondence

Address correspondence to Dr. Leung: Department of Anesthesia and Perioperative Care, University of California San Francisco, 500 Parnassus Avenue, Room MUE-415, San Francisco, California 94143–0648. Jacqueline.Leung@ucsf.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Appendix 1: Perioperative Medicine Research Group

The principal investigator is Jacqueline M. Leung, M.D., M.P.H. Research associates Stacey Chang, B.A., Gabriela Meckler, B.A., Stacey Newman, B.A., Tiffany Tsai, M.D., Vanessa Voss, M.D., and Emily Youngblom, B.A., participated in patient recruitment, cognitive assessments, data entry, and data management.

Appendix 2: Data Safety Monitoring

Data Safety Monitoring Board

Before the commencement of patient recruitment, we formed a data and safety monitoring board to monitor participant safety and data quality and to evaluate the progress of the study. The data and safety monitoring board focused on performance (subject recruitment, retention, and follow-up; flow of data forms; protocol adherence; and quality of data) and safety (magnitude and frequency of adverse events were measured).

Grading Method and Attribution for Adverse Event Reporting
Adverse events (AEs) were graded by the principal investigator using the 0- to 5-point scale where 0 = no AE or within normal limits or not clinically significant; 1 = mild AE, did not require treatment; 2 = moderate AE, resolved with treatment; 3 = severe AE, resulted in inability to carry on normal activities and required professional medical attention; 4 = life-threatening or disabling AE; and 5 = fatal AE. The principal investigator, who was blinded to the study group assignments, determined the relationship of AEs to the test study drug as one of the following: not related, possibly related, and definitely related.

Description of Anticipated Adverse Events
Sedation (evaluated by the Richmond Agitation and Sedation Scale), dizziness (patient self-report), ataxia, and nystagmus were adverse outcomes reported previously for patients treated with gabapentin.

Safety Data Evaluated
The data that were evaluated included but were not limited to subject interview, vital signs, physical examination results, clinical test results such as creatinine, and postoperative analgesic dosages.

Adverse Event Reporting
All serious adverse events (both anticipated and unanticipated) were reported to the University of California San Francisco Committee on Human Research, and National Institutes of Health (San Francisco, California).

Events that May Cause Termination/Dropout of a Participant from the Study
Adverse events (anticipated or unanticipated), subject's unwillingness to continue with the study, or treating physician's request were included.

Data and Safety Monitoring Board Meetings
A total of three data and safety monitoring board meetings were conducted throughout the study period to evaluate safety (first meeting), efficacy (second meeting, results blinded to the investigators), and final report (third meeting).

Stopping Rules
Early stopping rule was based on the development of prohibitive toxicity by the treatment. Reduction in postoperative delirium alone was not used as the sole early stopping criterion, because the standard treatment (typically opioids) was not considered to be an unsatisfactory option at present. Other reasons for termination of that study included poor accrual, significant negative effect of the treatment on the primary outcome, and excessive loss to follow-up.

Interim analyses focused on whether the death and adverse event rates for patients in this study exceeded the current in-hospital rates for this surgical population at our institution. Evidence of overwhelming efficacy was determined by statistically comparing the rate of delirium between the placebo and treatment groups. We used the O'Brien–Fleming guidelines for stopping due to overwhelming evidence of efficacy,[42] in which more stringent P values were used to determine stopping earlier in the trial compared with later in the trial.

Statistical results were not the sole basis for the decision to stop or continue the trial.[43] Additional factors used in consideration of termination of the intervention included the need for evaluation of this medication in the surgical setting given its pervasive off-label use in surgical patients in the postoperative period. Currently no large-scale experimental evidence exists regarding a variety of patient outcomes associated with use of this drug in the surgical setting. Therefore, the interim analyses included other important clinical outcomes in addition to the effect of the intervention on postoperative delirium, such as sedation and other possible drug-related side effects. Another factor to be considered included the effectiveness in lowering pain when compared with the placebo-treated patients.

Appendix 3: Opioid Conversion to Morphine Equivalents

Narcotic (administration), mg	Morphine 10 mg IV/IM Equivalent, mg
Butorphanol (IV/IM)	1–3
Codeine (IV/IM)	120–130
Codeine (PO)	200
Fentanyl (IV)	0.1
Hydrocodone (PO)	30–45
Hydromorphone (IV)	1.5
Hydromorphone (PO)	7.5
Levorphanol (IV/IM)	2
Levorphanol (PO)	4
Meperidine (IV/IM)	75
Meperidine (PO)	300
Methadone (IV/IM)	10
Methadone (PO)	12.5
Morphine (IV/IM)	10
Morphine (PO)	30
Nalbuphine (IV/IM)	10–12
Pentazocine (IV/IM)	30–60
Pentazocine (PO)	180

IM = intramuscular; IV = intravenous; PO = oral.

Appendix 4: Definitions of Nonfatal Postoperative Complications

In-hospital course was followed daily until discharge for the new occurrence of postoperative outcomes, which included ischemic cardiac complications (new occurrence of chest pain, electrocardiogram changes, or cardiac enzyme changes), clinically diagnosed myocardial infarction, dysrhythmias, and heart failure or clinically significant respiratory complications (pulmonary edema, tracheal reintubation, pulmonary consolidation on chest x-ray, pneumothorax, or pleural effusion). *Renal insufficiency* was defined as a new requirement of dialysis postoperatively or elevation of serum creatinine. *Neurologic event* was defined as new occurrence of transient ischemic attack or stroke, delirium, or confusion. Infection required documentation by a positive culture. *Gastrointestinal event* was defined as bowel ischemia, perforation, bleeding, cholecystitis or pancreatitis, or elevated postoperative liver enzymes with or without postoperative jaundice. *Thromboembolic event* was defined as deep venous thrombosis or pulmonary embolism. Other postoperative outcomes measured included death, surgical complications, and reoperation during the same hospitalization.[31]

References

1. Tsai TL, Sands LP, Leung JM: An update on postoperative cognitive dysfunction. Adv Anesth 2010; 28:269–84

2. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM: Postoperative delirium: The importance of pain and pain management. Anesth Analg 2006; 102:1267–73

3. Leung JM, Sands LP, Rico M, Petersen KL, Rowbotham MC, Dahl JB, Ames C, Chou D, Weinstein P: Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology 2006; 67:1251–3

4. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41

5. Berry JD, Petersen KL: A single dose of gabapentin reduces acute pain and allodynia in patients with herpes zoster. Neurology 2005; 65:444–7

6. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q: The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002; 95:985–91

7. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB: A randomized study of the effects of single-dose gabapentin *versus* placebo on postoperative pain and morphine consumption after mastectomy. ANESTHESIOLOGY 2002; 97:560–4

8. Turan A, Karamanlioğlu B, Memiş D, Hamamcioglu MK, Tükenmez B, Pamukçu Z, Kurt I: Analgesic effects of gabapentin after spinal surgery. ANESTHESIOLOGY 2004; 100:935–8

9. Turan A, Karamanlioğlu B, Memiş D, Usar P, Pamukçu Z, Türe M: The analgesic effects of gabapentin after total abdominal hysterectomy. Anesth Analg 2004; 98:1370–3

10. Dierking G, Duedahl TH, Rasmussen ML, Fomsgaard JS, Møiniche S, Rømsing J, Dahl JB: Effects of gabapentin on postoperative morphine consumption and pain after abdominal hysterectomy: A randomized, double-blind trial. Acta Anaesthesiol Scand 2004; 48:322–7

11. Rorarius MG, Mennander S, Suominen P, Rintala S, Puura A, Pirhonen R, Salmelin R, Haanpää M, Kujansuu E, Yli-Hankala A: Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. Pain 2004; 110:175–81

12. Dahl JB, Mathiesen O, Møiniche S: 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in in the treatment of postoperative pain. Acta Anaesthesiol Scand 2004; 48:1130–6

13. Gilron I, Orr E, Tu D, O'Neill JP, Zamora JE, Bell AC: A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy. Pain 2005; 113:191–200

14. Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB, Singh U, Singh PK: Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: A randomized, double-blind, placebo-controlled study. J Neurosurg Anesthesiol 2005; 17:65–8

15. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M: Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg 2005; 100:1394–9

16. Brandt J, Spencer M, Folstein M: The telephone interview for cognitive status. Neuropsychiatry Neuropsychol Behav Neurol 1988; 1: 111–7

17. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI: Clarifying confusion: The Confusion Assessment Method–A new method for detection of delirium. Ann Intern Med 1990; 113:941–8

18. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK: The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002; 166:1338–44

19. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S: The Memorial Delirium Assessment Scale. J Pain Symptom Manage 1997; 13:128–37

20. Shaheen PE, Walsh D, Lasheen W, Davis MP, Lagman RL: Opioid equianalgesic tables: Are they all equally dangerous? J Pain Symptom Manage 2009; 38:409–17

21. Swarm R, Abernethy AP, Anghelescu DL, Benedetti C, Blinderman CD, Boston B, Cleeland C, Coyle N, Deleon-Casasola OA, Eilers JG, Ferrell B, Janjan NA, Karver SB, Levy MH, Lynch M, Moryl N, Murphy BA, Nesbit SA, Oakes L, Obbens EA, Paice JA, Rabow MW, Syrjala KL, Urba S, Weinstein SM; NCCN Adult Cancer Pain: Adult cancer pain. J Natl Compr Canc Netw 2010; 8:1046–86

22. Wu CL, Hsu W, Richman JM, Raja SN: Postoperative cognitive function as an outcome of regional anesthesia and analgesia. Reg Anesth Pain Med 2004; 29:257–68

23. American Society of Anesthesiologists: ASA Physical Status Classification System. Available at: https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system. Accessed July 10, 2017

24. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987; 40:373–83

25. Sheikh J, Yesavage J: Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version, Clinical Gerontology, A Guide to Assessment and Intervention. Edited by Brink T. New York, The Haworth Press, 1986, pp 165–73

26. Leung JM, Sands LP, Lim E, Tsai TL, Kinjo S: Does preoperative risk for delirium moderate the effects of postoperative pain and opiate use on postoperative delirium? Am J Geriatr Psychiatry 2013; 21:946–56

27. ACC/AHA guideline update for the perioperative cardiovascular evaluation for noncardiac surgery: Executive summary–A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Anesth Analg 2002; 94:1052–64

28. Leung JM, Dzankic S: Relative importance of preoperative health status *versus* intraoperative factors in predicting

postoperative adverse outcomes in geriatric surgical patients. J Am Geriatr Soc 2001; 49:1080–5

29. Manku K, Bacchetti P, Leung JM: Prognostic significance of postoperative in-hospital complications in elderly patients: I–Long-term survival. Anesth Analg 2003; 96:583–9

30. Leung J, Sands L, Rico M, Petersen K, Rowbotham M, Dahl J, Ames C, Chou D, Weinstein P: Pilot clinical trial of gabapentin to decrease postoperative delirium in older surgical patients. Neurology 2006; 67:1–3

31. Fukata S, Kawabata Y, Fujisiro K, Katagawa Y, Kuroiwa K, Akiyama H, Terabe Y, Ando M, Kawamura T, Hattori H: Haloperidol prophylaxis does not prevent postoperative delirium in elderly patients: A randomized, open-label prospective trial. Surg Today 2014; 44:2305–13

32. Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, Pun BT, Thompson JL, Shintani AK, Meltzer HY, Bernard GR, Dittus RS, Ely EW; MIND Trial Investigators: Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: The MIND randomized, placebo-controlled trial. Crit Care Med 2010; 38:428–37

33. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, Eikelenboom P, van Gool WA: Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: A randomized placebo-controlled study. J Am Geriatr Soc 2005; 53:1658–66

34. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM: Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: A systematic review and meta-analysis. J Am Geriatr Soc 2016; 64:705–14

35. Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, Simpkins SA: Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev 2016; 3:CD005563

36. Gareri P, Segura-García C, Manfredi VG, Bruni A, Ciambrone P, Cerminara G, De Sarro G, De Fazio P: Use of atypical antipsychotics in the elderly: A clinical review. Clin Interv Aging 2014; 9:1363–73

37. Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Byrne AJ, Hudetz AG, Warltier DC, Pagel PS: Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2009; 23:651–7

38. Djaiani G, Silverton N, Fedorko L, Carroll J, Styra R, Rao V, Katznelson R: Dexmedetomidine *versus* propofol sedation reduces delirium after cardiac surgery: A randomized controlled trial. Anesthesiology 2016; 124:362–8

39. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, Zhu X, Zhu SN, Maze M, Ma D: Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: A randomised, double-blind, placebo-controlled trial. Lancet 2016; 388:1893–902

40. Jia Y, Jin G, Guo S, Gu B, Jin Z, Gao X, Li Z: Fast-track surgery decreases the incidence of postoperative delirium and other complications in elderly patients with colorectal carcinoma. Langenbecks Arch Surg 2014; 399:77–84

41. Lundström M, Olofsson B, Stenvall M, Karlsson S, Nyberg L, Englund U, Borssén B, Svensson O, Gustafson Y: Postoperative delirium in old patients with femoral neck fracture: A randomized intervention study. Aging Clin Exp Res 2007; 19:178–86

42. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM: Reducing delirium after hip fracture: A randomized trial. J Am Geriatr Soc 2001; 49:516–22

43. Sieber FE, Gottshalk A, Zakriya KJ, Mears SC, Lee H: General anesthesia occurs frequently in elderly patients during propofol-based sedation and spinal anesthesia. J Clin Anesth 2010; 22:179–83

44. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group: BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013; 25:33–42

45. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD: Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013; 110(suppl 1):i98–105

46. Fritz BA, Kalarickal PL, Maybrier HR, Muench MR, Dearth D, Chen Y, Escallier KE, Ben Abdallah A, Lin N, Avidan MS: Intraoperative electroencephalogram suppression predicts postoperative delirium. Anesth Analg 2016; 122:234–42

47. Kinjo S, Lim E, Sands LP, Bozic KJ, Leung JM: Does using a femoral nerve block for total knee replacement decrease postoperative delirium? BMC Anesthesiol 2012; 12:4

48. Mouzopoulos G, Vasiliadis G, Lasanianos N, Nikolaras G, Morakis E, Kaminaris M: Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: A randomized placebo-controlled study. J Orthop Traumatol 2009; 10:127–33

49. Arumugam S, Lau CS, Chamberlain RS: Use of preoperative gabapentin significantly reduces postoperative opioid consumption: A meta-analysis. J Pain Res 2016; 9:631–40