ANESTHESIOLOGY

# Cognitive Effects of Perioperative Pregabalin

## Secondary Exploratory Analysis of a Randomized Placebo-controlled Study

Marianne Myhre, M.D., Henrik Børsting Jacobsen, Psy.D., Ph.D., Stein Andersson, Ph.D., Audun Stubhaug, M.D., D.Med.Sci.

*ANESTHESIOLOGY 2019; 130:63–71*


## ABSTRACT

**Background:** Pregabalin has shown opioid sparing and analgesic effects in the early postoperative period; however, perioperative effects on cognition have not been studied. A randomized, parallel group, placebo-controlled investigation in 80 donor nephrectomy patients was previously performed that evaluated the analgesic, opioid-sparing, and antihyperalgesic effects of pregabalin. This article describes a secondary exploratory analysis that tested the hypothesis that pregabalin would impair cognitive function compared to placebo.

**Methods:** Eighty patients scheduled for donor nephrectomy participated in this randomized, placebo-controlled study. Pregabalin (150 mg twice daily, n = 40) or placebo (n = 40) was administered on the day of surgery and the first postoperative day, in addition to a pain regimen consisting of opioids, steroids, local anesthetics, and acetaminophen. Specific cognitive tests measuring inhibition, sustained attention, psychomotor speed, visual memory, and strategy were performed at baseline, 24 h, and 3 to 5 days after surgery, using tests from the Cambridge Neuropsychological Test Automated Battery.

**Results:** In the spatial working memory within errors test, the number of errors increased with pregabalin compared to placebo 24 h after surgery; median (25th, 75th percentile) values were 1 (0, 6) *versus* 0 (0, 1; rate ratio [95% CI], 3.20 [1.55 to 6.62]; $P = 0.002$). Furthermore, pregabalin significantly increased the number of errors in the stop-signal task stop-go test compared with placebo; median (25th, 75th percentile) values were 3 (1, 6) *versus* 1 (0, 2; rate ratio, 2.14 [1.13 to 4.07]; $P = 0.020$). There were no significant differences between groups in the paired associated learning, reaction time, rapid visual processing, or spatial working memory strategy tests.

**Conclusions:** Perioperative pregabalin significantly negatively affected subdomains of executive functioning, including inhibition, and working memory compared to placebo, whereas psychomotor speed was not changed.

(ANESTHESIOLOGY 2019; 130:63–71)


## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Perioperative administration of pregabalin has been associated with decreased postoperative pain and opioid requirements

### What This Article Tells Us That Is New

- This secondary analysis of data demonstrating that perioperative administration of pregabalin was associated with a reduction in opioid requirements and incisional hyperalgesia suggests that these benefits may be compromised by an increased risk of developing impaired postoperative cognitive performance

Pregabalin is increasingly used for the treatment of early postoperative pain as part of a multimodal pain regimen.[1] Its predecessor, gabapentin, was developed for the treatment of epilepsy,[2] but later gabapentin and pregabalin were also approved for the treatment of neuropathic pain conditions, generalized anxiety disorders, and fibromyalgia.[3] The justification for pregabalin perioperatively in multimodal pain treatment is determined based on analgesic efficacy and total burden of adverse effects.

Recently, there has been increased focus on adverse effects associated with the use of pregabalin.[4,5] Side effects, including somnolence, dizziness, visual disturbances, and ataxia, are frequently reported,[6,7] and recently, respiratory depressive effects have also been described.[8,9] Despite well-known central nervous system adverse effects, the cognitive effects of perioperatively administered pregabalin have not been investigated. Several factors, such as age, educational level, and preoperative mental health, are recognized as factors that contribute to early postoperative cognitive impairment.[10,11]

Postoperative cognitive dysfunction is not clearly defined in the literature but differs from postoperative delirium because it is more subtle and longer lasting.[12,13] Therefore, postoperative cognitive dysfunction may only be identified through specific and sensitive neuropsychological tests[14] that measure processes like attention, working memory, decision-making, inhibition, psychomotor speed, and mental flexibility.[15] The umbrella term "executive function" encompasses these processes and is regarded as essential for goal-directed behavior in which attentional functions like alerting, orienting, and executive control and their

This article is featured in "This Month in Anesthesiology," page 1A. This article has a visual abstract available in the online version.

Submitted for publication January 13, 2018. Accepted for publication September 6, 2018. From the Department of Pain Management and Research (H.B.J., A.S.), Department of Anesthesiology, Division of Emergencies and Critical Care (M.M.), Oslo University Hospital, Rikshospitalet, Oslo, Norway; and the Institute of Medicine, Faculty of Medicine (M.M., A.S.) and the Department of Psychology (S.A.), University of Oslo, Oslo, Norway.







<zdoi;10.1097/ALN.0000000000002473>

interactions play important roles.[16] Moreover, executive function is essential for appropriate decision-making and impulse control,[17] making it a crucial factor in risk of reinjury and impulsive actions after surgery.

We previously performed a randomized, parallel group investigation in 80 donor nephrectomy patients that evaluated the analgesic, opioid-sparing, and antihyperalgesic effects of pregabalin.[18] In the this article, we present a secondary exploratory analysis of previously unpublished data of cognitive test performance in the same patients.

The aim of this study was to explore the cognitive effects of 150 mg of pregabalin—administered twice daily, on the day of surgery and on the subsequent day—using neuropsychological tests suitable for repeated assessments measuring visual memory, working memory, executive function, and attention. We hypothesized that pregabalin, relative to placebo, administered as part of a multimodal pain regimen consisting of opioids, steroids, local anesthetics, and acetaminophen, would affect executive functioning, including inhibition, strategic thinking, mental flexibility, working memory, and processing speed.

## Materials and Methods

Approval for this study was obtained from the Regional Committee for Medical Research Ethics for Eastern Norway, Oslo, Norway, and the Norwegian Medicines Agency, Oslo, Norway, and was also registered at EudraCT (2009-015316-17) and www.ClinicalTrials.gov (NCT01059331, January 28, 2010). The study is reported in accordance with the Consolidated Standards of Reporting Trials Statement[19] for randomized trials and conducted in compliance with the Declaration of Helsinki. Eighty patients with American Society of Anesthesiologists classification I or II scheduled for elective laparoscopic donor nephrectomy were included. After a written consent, the patients were randomized to one of two treatment groups: 150 mg of pregabalin or placebo was administered two times daily over two consecutive days (totaling 600 mg), starting in the morning before surgery. Standard postoperative analgesic treatment was administered comprising local anesthetic wound infiltration, a single dose of dexamethasone, acetaminophen regularly, and opioids (ketobemidone) as required. The analgesic, opioid-sparing, and antihyperalgesic effects of pregabalin in the same study population have been extensively reported in the primary publication.[18] Details on inclusion and exclusion criteria, randomization, blinding, drug preparation, anesthesia, and perioperative treatment are also previously published.[18]

Cognitive function was measured using tests selected from the Cambridge Neuropsychological Test Automated Battery, a computer-based test battery assessing different domains of cognitive functioning, including executive function, attention, and psychomotor speed.[20] The tests were performed using a computer tablet and a press pad. During the test period, the patients were seated in an upright comfortable position with the computer tablet arranged on a table at a 50-cm distance, with the press pad placed on the table in front of the computer, allowing the patient's dominant hand and arm to rest comfortably beneath it. The test battery included six different tests selected *a priori* based on earlier studies on cognitive functioning in patients treated with pregabalin.[8]

### Motor Screening

The motor screening test screens for visual, movement, and comprehension difficulties. It is administered to introduce the patient to the computer, the touch screen, and the press pad and is a prerequisite for administering the test battery. This test was not used for subsequent statistical analysis.

### Reaction Time

The reaction time test measures response speed when a yellow spot appears in the center of the screen or in five different locations on the screen, and the subject must react to the stimulus by releasing the press pad button and touching the screen where the spot appeared. The relationship between cognitive functions and physical movements are then used to calculate psychomotor speed. We used the following outcome: reaction time, five-choice, which measures the psychomotor speed.

### Paired Associated Learning

The paired associated learning test assesses visual learning and recognition memory by displaying six to eight boxes on the screen that are opened in a randomized order. The patterns shown in the boxes are then displayed in the middle of the screen, and the subject has to remember in which box the pattern was originally located. The test has five stages with increasing memory loads, specifically, increasing the numbers of patterns from two to eight. We used the following outcome: paired associated learning, total errors (six shapes), adjusted for each stage not attempted because of previous failure.

### Rapid Visual Information Processing

The rapid visual processing test measures a subdomain of sustained attention, evaluating both continuous performance and visual sustained attention. In this test, a digit from 2 to 9 appears in a pseudorandom order at a rate of 100 digits/min. The patients are requested to detect three different target sequences of digits by pressing the response button. We used the following outcome: rapid

visual processing A', measuring the sensitivity to the target regardless of response tendency.

### Spatial Working Memory

The spatial working memory test assesses the ability to implement strategic thinking for problem-solving. The test has notable executive function demands and provides a measure of strategy as well as working memory errors. In this test, several boxes are displayed on the screen. The subject is required to search for one blue token in each of the boxes by the process of elimination. The number of boxes increases from three to eight. The existence of a predefined search strategy was examined.[21] A high score indicates poor strategy, whereas a low score indicates an effective use of strategy. We used the following outcome measures: (1) spatial working memory within errors, four to eight boxes, defined as the number of times the patient revisits a box already found to be empty, and (2) spatial working memory strategy, defined as the number of times a new search begins with a different box.

### Stop-signal Task

The stop-signal task test is an executive function task measuring response inhibition and impulsivity. In this go/no-go task, a circle is shown on the screen. After a fixed delay, an arrow pointing to the left or right is displayed within the circle. The subjects are requested to press the left or right press pad button according to the direction of the arrow. In the second part of the test, the patients are asked to withhold their response when they hear an auditory signal. We used the following outcome: stop-signal task stop-go, measuring the number of direction errors on stop-and-go trials.

The cognitive test battery was administered three times during the hospital stay. The first assessment was conducted 1 to 3 days before surgery and served as a baseline. The second test was performed during the day 24 h after surgery, whereas the third assessment was completed 3 to 5 days postoperatively and at least 36 h after the final administration of the test drug. The primary outcomes of interest were the difference between the pregabalin group and the placebo group from baseline to 24 h after surgery for all six neurocognitive tests. Premorbid intelligence was estimated using a Norwegian version of the National Adult Reading Test.[22]

### Statistical Analysis

The sample size is based on a previous study of the same study population investigating the opioid sparing and analgesic effect of pregabalin.[18] In this earlier study, 20% difference in opioid usage was considered clinically relevant. With mean opioid consumption of 50 mg and SD of 15 in the control group, a two-sided $\alpha = 0.05$ and a statistical power of 0.8, 36 participants were required in each group. To compensate for dropouts, 80 participants were included. The effect of pregabalin on cognitive outcomes in the early postoperative period has not been well studied. Thus, this study must be considered exploratory with respect to cognitive outcome measures. Participant demographics and intraoperative data were summarized and stratified according to treatment groups as mean (± SD) and numbers, as appropriate and independent samples *t* tests and chi-square for independence tests were used to test for group differences. Mixed-effect negative binomial regression was used to fit overdispersed count data (spatial working memory within errors, stop-signal task stop-go, paired associated learning), and the linear mixed-effects model was used for normal distributed continuous data (spatial working memory strategy, rapid visual processing A', reaction time). In the models, treatment groups, time, and treatment-by-time interactions were defined as fixed effects, whereas subjects were treated as a random effect accounting for repeated measurements within patients. To test our hypothesis, we estimated the difference between the change from baseline to 24 h after surgery in the pregabalin group and the change from baseline to 24 h after surgery in the placebo group using the placebo as the reference group. The results were reported as rate ratios and estimated mean differences, with 95% CI. Although not of primary interest, we also explored differences between the groups from 24 h after surgery to 3 to 5 days after surgery in a secondary analysis. Data analyses were performed with IBM SPSS Statistics 25 (SPSS Inc., USA).

## Results

The study was performed at Oslo University Hospital, Rikshospitalet, Norway, between February 2010 and October 2012. In total, 80 patients, 55 females and 25 males, scheduled for elective donor nephrectomy were randomized. All 80 patients completed the study, with a limited number of protocol deviations (fig. 1). One patient in the pregabalin group received inhalation anesthesia with sevoflurane 90 min before switching to total intravenous anesthesia, whereas one patient received erroneously higher boluses of opioids from the patient-controlled analgesic device and was treated with naloxone. Seven patients in the placebo group and one patient in the pregabalin group refused testing 24 h after surgery because of nausea and pain. One patient in the placebo group refused the last test 3 to 5 days after surgery as well as further participation, because of complaints about discomfort and pain. The treatment groups were comparable in terms of age, sex, education, Norwegian

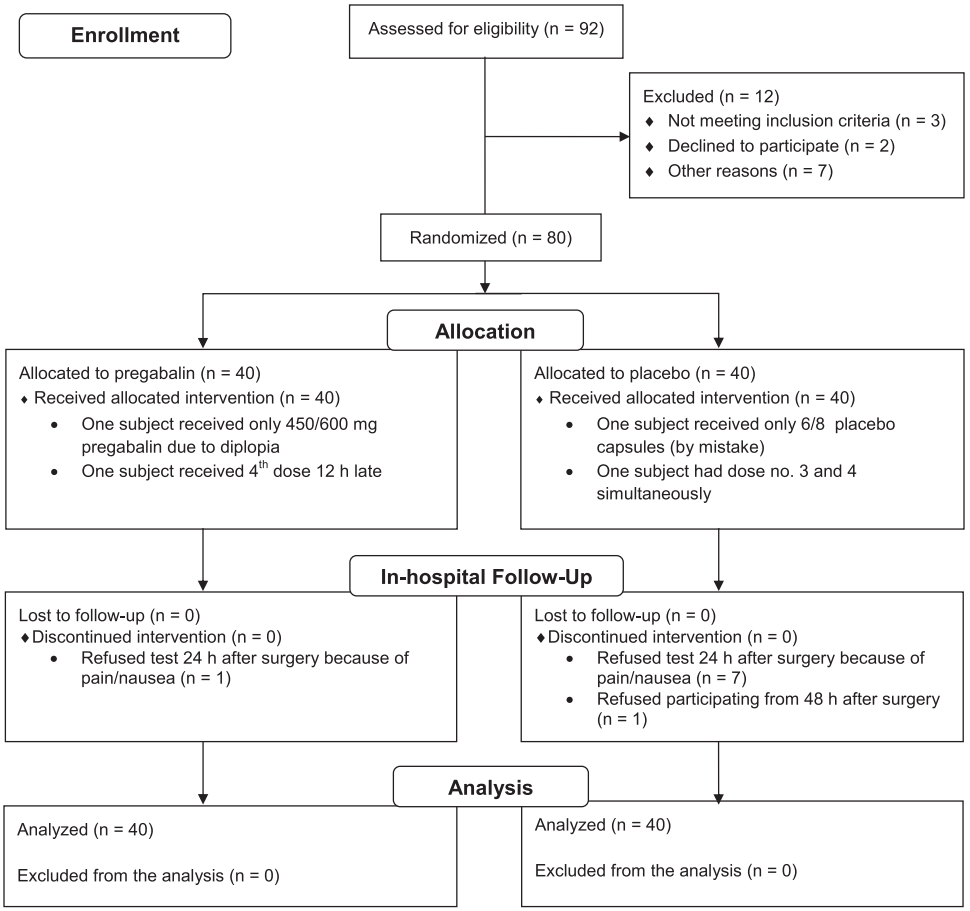


**Fig. 1.** Consolidated Standards of Reporting Trials flowchart of enrollment, treatment allocation, and analysis.

National Adult Reading Test scores, and intraoperative data (table 1).

Cognitive functioning was evaluated using six different neurocognitive tests. Descriptive data presented as median and 25th and 75th percentiles at baseline, 24 h after surgery, and 3 to 5 days after surgery are shown in table 2. In the spatial working memory within errors test, the number of errors increased significantly from baseline to 24 h after surgery in the pregabalin group compared with the placebo group (rate ratio [95% CI], 3.20 [1.55 to 6.62]; $P = 0.002$; table 3). Similarly, in the stop-signal task stop-go test, the number of errors increased significantly from baseline to 24 h after surgery in the pregabalin group compared with placebo (rate ratio, 2.14 [1.13 to 4.07]; $P = 0.020$; table 3). In the time period from 24 h after surgery to 3 to 5 days after surgery, the difference between the pregabalin and placebo groups in the spatial working memory within error test (rate ratio, 0.43 [0.21 to 0.88]; $P = 0.022$), as well as the stop-signal task stop-go trial (rate ratio, 0.28 [0.16 to 0.50]; $P < 0.001$), reduced significantly. In the paired associated learning, spatial working memory strategy, reaction time, and rapid visual processing A' tests, the differences between the pregabalin group and the placebo group were not significant (table 3).

**Table 1.** Demographics and Intraoperative Data

| | Pregabalin ($n = 40$) | Placebo ($n = 40$) |
|---|---|---|
| Age, yr | 47 ± 11 | 47 ± 14 |
| Sex, male/female | 12/28 | 13/27 |
| Education, n (0–12 yr/13–15 yr/16–17 yr) | 23/9/8 | 18/18/4 |
| Norwegian National Adult Reading Test, no. of errors | 16 ± 8 | 17 ± 10 |
| Weight, kg | 74.5 ± 14.5 | 72.0 ± 12.5 |
| Propofol, mg | 1,514 ± 504 | 1,679 ± 629 |
| Remifentanil, mg | 3.9 ± 1.3 | 4.2 ± 1.6 |
| Duration of anesthesia, min | 207 ± 27 | 209 ± 30 |
| Duration of surgery, min | 140 ± 23 | 143 ± 29 |

The data are presented as means ± SD and numbers. No significant differences were found between the treatment groups. The level of significance was $P < 0.05$.

**Table 2.** Descriptive Data for All Neurocognitive Tests

| | Baseline | 24 h after Surgery | 3–5 Days after Surgery |
|---|---|---|---|
| Paired associated learning, no. of errors | | | |
| Pregabalin | 3 (1, 7) | 4 (0, 9) | 3 (0, 4) |
| Placebo | 6 (3, 10) | 6 (2, 11) | 3 (1, 6) |
| Spatial working memory within errors, no. of errors | | | |
| Pregabalin | 1 (0, 5) | 1 (0, 6) | 1 (0, 3) |
| Placebo | 1 (0, 6) | 0 (0, 1) | 1 (0, 2) |
| Stop-signal task stop-go, no. of errors | | | |
| Pregabalin | 1 (0, 4) | 3 (1, 6) | 1 (0, 2) |
| Placebo | 1 (0, 3) | 1 (0, 2) | 1 (0, 3) |
| Spatial working memory strategy, no. | | | |
| Pregabalin | 34 (30, 38) | 33 (28, 37) | 33 (26, 37) |
| Placebo | 35 (33, 37) | 34 (30, 37) | 34 (30, 37) |
| Rapid visual processing A' (range, 0.00–1.00) | | | |
| Pregabalin | 0.91 (0.87, 0.94) | 0.91 (0.86, 0.95) | 0.93 (0.90, 0.95) |
| Placebo | 0.90 (0.86, 0.94) | 0.89 (0.86, 0.92) | 0.93 (0.87, 0.95) |
| Reaction time, ms | | | |
| Pregabalin | 322 (295, 350) | 328 (304, 367) | 342 (308, 369) |
| Placebo | 315 (296, 349) | 332 (309, 375) | 331 (300, 354) |

The data are presented as medians and 25th and 75th percentiles.

**Table 3.** Neurocognitive Tests

| | Time | Exp (β) or Mean | 95% CI | *P* Value |
|---|---|---|---|---|
| Paired associated learning, no. of errors | Baseline to 24 h | 1.48* | 0.86 to 2.55 | 0.16 |
| | 24 h to 3–5 days | 0.89* | 0.52 to 1.52 | 0.68 |
| Spatial working memory within errors, no. of errors | Baseline to 24 h | 3.20* | 1.55 to 6.62 | 0.002 |
| | 24 h to 3–5 days | 0.43* | 0.21 to 0.88 | 0.02 |
| Stop-signal task stop-go, no. of errors | Baseline to 24 h | 2.14* | 1.13 to 4.07 | 0.02 |
| | 24 h to 3–5 days | 0.28* | 0.16 to 0.50 | <0.001 |
| Spatial working memory strategy, no. | Baseline to 24 h | −1.29† | −3.82 to 1.26 | 0.38 |
| | 24 h to 3–5 days | −1.55† | −4.22 to 1.13 | 0.25 |
| Rapid visual processing A' (range, 0.00–1.00) | Baseline to 24 h | 0.02† | −0.01 to 0.04 | 0.23 |
| | 24 h to 3–5 days | 0.02† | −0.01 to 0.04 | 0.21 |
| Reaction time, ms | Baseline to 24 h | −1.35† | −22.36 to 19.66 | 0.90 |
| | 24 h to 3–5 days | 8.17† | −12.90 to 29.24 | 0.44 |

Changes from baseline to 24 h after surgery and from 24 h after surgery to 3 to 5 days after surgery for pregabalin relative to placebo are shown. The data are presented as rate ratios (pregabalin/placebo), means, and 95% CI. The level of significance was $P < 0.05$. Mixed-effect negative binomial regression and linear mixed models were used to estimate the differences between groups. In the spatial working memory within errors and the stop-signal task stop-go test, the test performance in the pregabalin group was significantly impaired from baseline to 24 h after surgery compared with the placebo group.

*Exponential (β). †Mean.

## Discussion

In this randomized controlled trial, the cognitive effects of perioperative pregabalin were assessed using neurocognitive tests measuring different aspects of memory, attention, and executive functions. We found that in tests of inhibition and working memory, performance was significantly impaired by the perioperative administration of pregabalin when compared to placebo.

More specifically, the results showed a significantly impaired performance in the pregabalin group in the spatial working memory within error test. This test assesses visuospatial working memory and strategic choices,[23] which are important for performance of higher cognitive functions.[24]

Impulsivity and inhibitory functions were measured using the stop-signal task stop-go test.[25] The results in this study showed a significant increase in the number

of errors in the pregabalin group. Poor inhibition has been linked to decreased motor control and increased risk of falling in elderly patients and those with mild dementia.[26,27]

In the reaction time five-choice test, a test of processing speed and attention, both groups showed significantly reduced performance from baseline to 24 h after surgery, although the difference between the two groups was not significant. Earlier studies have demonstrated that opioids reduce processing speed compared to placebo.[28,29] Patients in this study required less opioids when treated with pregabalin. Nevertheless, both groups showed similar worse performance on the first postoperative day, indicating that pregabalin may also contribute to reduced psychomotor speed.

The cognitive effects of pregabalin have been investigated in animal models[30] and in human preclinical models. In a crossover study in healthy volunteers by Hindmarch *et al.*,[31] the cognitive and psychomotor effects of 150 mg of pregabalin (three times a day) for 3 days were investigated, using alprazolam and placebo as a positive comparator and control, respectively. Pregabalin showed limited negative effects in tests assessing arousal (critical flicker fusion) and attention (compensatory tracking task), but no significant effects in psychometrics compared with placebo were observed. In another study,[32] pregabalin was titrated more than 8 weeks to 600 mg/day and then maintained at this dose for an additional 4 weeks. Pregabalin impaired outcomes in half of the cognitive tests (digit symbol, Stroop, controlled oral word association), which was supported by subjective cognitive complaints in the patients treated with pregabalin. Furthermore, in a study by Ciesielski *et al.*,[33] the neuropsychological and psychiatric impact of 300 mg of pregabalin *versus* levetiracetam was investigated, and significantly reduced verbal and visual episodic memory was observed in patients treated with pregabalin compared to those treated with levetiracetam. Finally, in a crossover study[34] in young healthy volunteers, the psychomotor effect of 75 mg of pregabalin in combination with 10 mg of oxycodone orally was investigated. The results, however, did not reveal any significant psychomotor effect in performance on the test used. Thus, our results are in line with the findings in these studies suggesting that pregabalin may impair executive functions rather than psychomotor speed. Furthermore, control measurements without the test medication 3 to 5 days after surgery were similar between the treatment groups, implying that the cognitive impairments were transient.

Attentional functions such as being alert, orienting, and executive control are all important prerequisites for performing daily tasks and managing everyday life.[16] Furthermore, cognitive function plays an important role in the control of gait and balance.[35] In a systematic review and meta-analysis of the adverse events associated with pregabalin, disturbances related to coordination and cognition were the most common, indicating involvement of both vestibulocerebellar and brainstem structures, as well as higher cortical functions.[36] There was a clear dose–response relationship in the onset of adverse events, and most adverse events were observed at pregabalin doses of 300 mg/day. The authors concluded that the use of pregabalin may lead to balance disorders, lack of coordination, and increased risk of falling trauma.

In contrast to the studies mentioned above, the current study was a postoperative trial. The etiology of postoperative cognitive decline is not well elucidated, although multiple factors have been proposed, including surgery, use of analgesics, inflammation, sleep disturbances, comorbidity, and age.[37,38]

There is evidence that inflammation and pain interfere with cognitive function.[39] In our study population, pain intensities were generally low and similar between the treatment groups and did not significantly affect the cognitive test results. Preclinical and clinical studies suggest that the gabapentinoids alleviate pain by actions at both spinal and supraspinal sites.[40,41] Furthermore, supraspinal nociceptive processing and cognitive processing are assumed to be closely linked, with common neurotransmitters and anatomic structures.[42] The drugs used for multimodal pain treatment may therefore interact with both nociceptive and neurocognitive circuitry.[42] The evidence that opioids *per se* impair postoperative cognitive performance is scarce[43]; however, studies show that opioids disrupt sleep architecture, which may indirectly lead to reduced cognitive performance.[44] Nevertheless, in a previous study in healthy volunteers investigating the cognitive effects of 10 mg of oxycodone orally, the results revealed a significant decline in simple and sustained attention and working and verbal memory compared to baseline.[45] In the present study, inhibition and working memory were significantly affected when pregabalin was combined with opioids compared with opioids alone, even though the opioid dose required was lower in the pregabalin group compared to the placebo group. Hence, there is reason to believe that the combination of pregabalin and opioids may cause additive or even supraadditive cognitive impairments compared with the use of each drug alone.

Age, educational level, and prehospital mental state are all independent factors linked to postoperative cognitive decline.[46] Consequently, particularly susceptible groups, such as older patients and patients with different neurologic and psychiatric disorders, may be more sensitive to drugs like pregabalin negatively affecting cognition and coordination. Moreover, reduced renal function in older adults may require reduced dosage, as more than 89% of the drug is eliminated renally. The participants in the current study were all young or middle-aged kidney donors, and educational status and

Norwegian Adult Reading Test scores were comparable between the treatment groups. Nevertheless, the results indicate that even younger patients may be negatively affected by pregabalin.

There are some limitations to this study. First, this is an exploratory study in which we examined the effect of perioperative pregabalin on performance on six different cognitive tests without correcting for multiple testing.[47] When *P* values were corrected for multiple outcome variables using the Benjamini and Hochberg method[48] (software R, version 3.4.0[49]), the difference in the stop-signal task stop-go test disappeared ($P = 0.06$), whereas the difference in spatial working memory within error test was still significant ($P = 0.012$). Thus, our results require replication. Furthermore, the clinical relevance of our findings remains to be determined. We did not measure patients' self-reports of cognitive functioning. This could have supplemented our data.

In our study, only one dose of pregabalin was used; hence, the validity of our results is restricted to this dose and cannot be extrapolated to other doses. However, the dose of 300 mg of pregabalin daily used in this study is consistent with the recommended dose for the treatment of acute postoperative pain.[1,50] Moreover, pregabalin was only administered on the day of surgery and the day immediately after surgery; thus, the results are not valid for longer perioperative treatment periods. Some patients (seven in the placebo group and one in the pregabalin group) denied testing 24 h after surgery because of pain and nausea. Thus, our data are somewhat incomplete, which may have influenced the results. Finally, we did not obtain blood samples to measure pregabalin plasma concentrations; thus, potential pharmacokinetic interactions between pregabalin and ketobemidone cannot be completely eliminated. A pharmacokinetic drug–drug interaction is unlikely, however, because pregabalin is neither metabolized by nor bound to plasma proteins affecting the cytochrome P450 liver system.[2] In conclusion, this exploratory study found that perioperatively administered pregabalin negatively affects executive functioning by impairing working memory and inhibition, measured as neuropsychological task performance.

## Acknowledgments

The authors thank the many patients involved in this study; Leiv Arne Rosseland, M.D., Ph.D., Department of Anesthesia, Division of Emergencies and Critical Care, Oslo University Hospital, Rikshospitalet, Oslo, Norway, for kind assistance with randomization; and the surgical team, all affiliated with the Department of Transplantation Medicine, Oslo University Hospital, Rikshospitalet, Oslo Norway, for excellent support and collaboration – the surgeons for performing the operative procedures, and the nurses for drug handling and assistance with the registration of pain scores and adverse effects.

## Research Support

Supported by a scholarship from the University of Oslo, Norway, and funds from Inven2, a nonprofit research organization owned by Oslo University Hospital, Oslo, Norway (to Dr. Myhre).

## Competing Interests

The authors declare no competing interests.

## Reproducible Science

Full protocol available at: marianne.myhre@medisin.uio.no. Raw data available at: marianne.myhre@medisin.uio.no.

## Correspondence

Address correspondence to Dr. Myhre: Oslo University Hospital, Rikshospitalet, P.O. Box 4950, Nydalen, N-0424 Oslo, Norway. marianne.myhre@medisin.uio.no. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

## References

1. Mishriky BM, Waldron NH, Habib AS: Impact of pregabalin on acute and persistent postoperative pain: A systematic review and meta-analysis. Br J Anaesth 2015; 114:10–31
2. Ben-Menachem E: Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004; 45(suppl 6):13–8
3. Shneker BF, McAuley JW: Pregabalin: A new neuromodulator with broad therapeutic indications. Ann Pharmacother 2005; 39:2029–37
4. Kharasch ED, Eisenach JC: Wherefore gabapentinoids?: Was there rush too soon to judgment? Anesthesiology 2016; 124:10–2
5. Fabritius ML, Geisler A, Petersen PL, Nikolajsen L, Hansen MS, Kontinen V, Hamunen K, Dahl JB, Wetterslev J, Mathiesen O: Gabapentin for post-operative pain management: A systematic review with meta-analyses and trial sequential analyses. Acta Anaesthesiol Scand 2016; 60:1188–208
6. Eipe N, Penning J, Yazdi F, Mallick R, Turner L, Ahmadzai N, Ansari MT: Perioperative use of pregabalin for acute pain: A systematic review and meta-analysis. Pain 2015; 156:1284–300
7. Zaccara G, Gangemi PF, Cincotta M: Central nervous system adverse effects of new antiepileptic drugs: A

meta-analysis of placebo-controlled studies. Seizure 2008; 17:405–21
8. Myhre M, Diep LM, Stubhaug A: Pregabalin has analgesic, ventilatory, and cognitive effects in combination with remifentanil. Anesthesiology 2016; 124:141–9
9. Weingarten TN, Jacob AK, Njathi CW, Wilson GA, Sprung J: Multimodal analgesic protocol and postanesthesia respiratory depression during phase I recovery after total joint arthroplasty. Reg Anesth Pain Med 2015; 40:330–6
10. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS: Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008; 108:18–30
11. Krenk L, Rasmussen LS, Kehlet H: New insights into the pathophysiology of postoperative cognitive dysfunction. Acta Anaesthesiol Scand 2010; 54:951–6
12. Krenk L, Rasmussen LS: Postoperative delirium and postoperative cognitive dysfunction in the elderly: What are the differences? Minerva Anestesiol 2011; 77:742–9
13. Bryson GL, Wyand A: Evidence-based clinical update: General anesthesia and the risk of delirium and postoperative cognitive dysfunction. Can J Anaesth 2006; 53:669–77
14. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT; ISPOCD group. The International Study of Postoperative Cognitive Dysfunction: The assessment of postoperative cognitive function. Acta Anaesthesiol Scand 2001; 45:275–89
15. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD: The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: A latent variable analysis. Cogn Psychol 2000; 41:49–100
16. Mackie MA, Van Dam NT, Fan J: Cognitive control and attentional functions. Brain Cogn 2013; 82:301–12
17. Bechara A: Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. Nat Neurosci 2005; 8:1458–63
18. Myhre M, Romundstad L, Stubhaug A: Pregabalin reduces opioid consumption and hyperalgesia but not pain intensity after laparoscopic donor nephrectomy. Acta Anaesthesiol Scand 2017; 61:1314–24
19. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG; CONSORT: CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. Int J Surg 2012; 10:28–55
20. Fray PJ, Robbins TW: CANTAB battery: Proposed utility in neurotoxicology. Neurotoxicol Teratol 1996; 18:499–504
21. Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW: Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 1990; 28:1021–34
22. Nelson HE, Willison J: National adult reading test (NART), 2nd Edition. Windsor, UK, 1991, pp 1–26
23. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P: Cambridge Neuropsychological Test Automated Battery (CANTAB): A factor analytic study of a large sample of normal elderly volunteers. Dementia 1994; 5:266–81
24. Constantinidis C, Klingberg T: The neuroscience of working memory capacity and training. Nat Rev Neurosci 2016; 17:438–49
25. Verbruggen F, Logan GD: Response inhibition in the stop-signal paradigm. Trends Cogn Sci 2008; 12:418–24
26. Kearney FC, Harwood RH, Gladman JR, Lincoln N, Masud T: The relationship between executive function and falls and gait abnormalities in older adults: A systematic review. Dement Geriatr Cogn Disord 2013; 36:20–35
27. van der Wardt V, Logan P, Hood V, Booth V, Masud T, Harwood R: The association of specific executive functions and falls risk in people with mild cognitive impairment and early-stage dementia. Dement Geriatr Cogn Disord 2015; 40:178–85
28. Khodayari-Rostamabad A, Olesen SS, Graversen C, Malver LP, Kurita GP, Sjøgren P, Christrup LL, Drewes AM: Disruption of cortical connectivity during remifentanil administration is associated with cognitive impairment but not with analgesia. Anesthesiology 2015; 122:140–9
29. Münte S, Quaedflieg CW, Sambeth A, Wang M, Kalso E: Effects of remifentanil on cognitive and psychomotor functioning and mood. Br J Anaesth 2013; 111:517–8
30. Kawano T, Eguchi S, Iwata H, Yamanaka D, Tateiwa H, Locatelli FM, Yokoyama M: Pregabalin can prevent, but not treat, cognitive dysfunction following abdominal surgery in aged rats. Life Sci 2016; 148:211–9
31. Hindmarch I, Trick L, Ridout F: A double-blind, placebo- and positive-internal-controlled (alprazolam) investigation of the cognitive and psychomotor profile of pregabalin in healthy volunteers. Psychopharmacology (Berl) 2005; 183:133–43
32. Salinsky M, Storzbach D, Munoz S: Cognitive effects of pregabalin in healthy volunteers: A double-blind, placebo-controlled trial. Neurology 2010; 74:755–61
33. Ciesielski AS, Samson S, Steinhoff BJ: Neuropsychological and psychiatric impact of add-on titration of pregabalin *versus* levetiracetam: A comparative short-term study. Epilepsy Behav 2006; 9:424–31
34. Zacny JP, Paice JA, Coalson DW: Subjective, psychomotor, and physiological effects of pregabalin alone and in combination with oxycodone in healthy volunteers. Pharmacol Biochem Behav 2012; 100:560–5
35. Saverino A, Waller D, Rantell K, Parry R, Moriarty A, Playford ED: The role of cognitive factors in predicting

balance and fall risk in a neuro-rehabilitation setting. PLoS One 2016; 11:e0153469
36. Zaccara G, Gangemi P, Perucca P, Specchio L: The adverse event profile of pregabalin: A systematic review and meta-analysis of randomized controlled trials. Epilepsia 2011; 52:826–36
37. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS: Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators: International Study of Post-Operative Cognitive Dysfunction. Lancet 1998; 351:857–61
38. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA; Neurological Outcome Research Group and the Cardiothoracic Anesthesiology Research Endeavors Investigators: Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001; 344:395–402
39. Hudetz JA, Gandhi SD, Iqbal Z, Patterson KM, Pagel PS: Elevated postoperative inflammatory biomarkers are associated with short- and medium-term cognitive dysfunction after coronary artery surgery. J Anesth 2011; 25:1–9
40. Hayashida K, DeGoes S, Curry R, Eisenach JC: Gabapentin activates spinal noradrenergic activity in rats and humans and reduces hypersensitivity after surgery. Anesthesiology 2007; 106:557–62
41. Hayashida K, Obata H, Nakajima K, Eisenach JC: Gabapentin acts within the locus coeruleus to alleviate neuropathic pain. Anesthesiology 2008; 109:1077–84
42. Moriarty O, McGuire BE, Finn DP: The effect of pain on cognitive function: A review of clinical and preclinical research. Prog Neurobiol 2011; 93:385–404
43. Fong HK, Sands LP, Leung JM: The role of postoperative analgesia in delirium and cognitive decline in elderly patients: A systematic review. Anesth Analg 2006; 102:1255–66
44. Nelson AM, Battersby AS, Baghdoyan HA, Lydic R: Opioid-induced decreases in rat brain adenosine levels are reversed by inhibiting adenosine deaminase. Anesthesiology 2009; 111:1327–33
45. Cherrier MM, Amory JK, Ersek M, Risler L, Shen DD: Comparative cognitive and subjective side effects of immediate-release oxycodone in healthy middle-aged and older adults. J Pain 2009; 10:1038–50
46. Silbert B, Evered L, Scott DA, McMahon S, Choong P, Ames D, Maruff P, Jamrozik K: Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery. Anesthesiology 2015; 122:1224–34
47. Li G, Taljaard M, Van den Heuvel ER, Levine MA, Cook DJ, Wells GA, Devereaux PJ, Thabane L: An introduction to multiplicity issues in clinical trials: The what, why, when and how. Int J Epidemiol 2017; 46:746–55
48. Benjamini Y, Hochberg Y: Controlling the false discovery rate: A practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995; 57:289–300
49. R Development Core Team: R: A language and environment for statistical computing. Vienna, Austria, R Foundation for Statistical Computing, 2011
50. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu CL: Management of postoperative pain: A clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016; 17:131–57