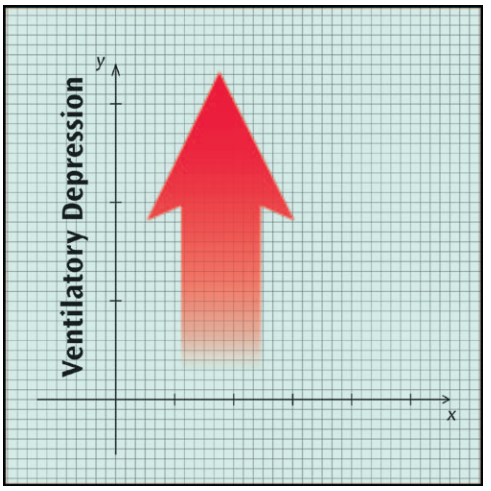
Wherefore Gabapentinoids?

Was There Rush Too Soon to Judgment?

Evan D. Kharasch, M.D., Ph.D., James C. Eisenach, M.D.

NEARLY a quarter century ago, a group of Scandinavian investigators raised global awareness of the deadly risk of respiratory depression from a novel perioperative analgesic method: neuraxial morphine.[1] Postoperative respiratory depression from opioids remains a concern today, and in this month's issue of ANESTHESIOLOGY, a different group of Scandinavian investigators raises concern of a potentially dangerous drug interaction with application of multimodal analgesia.[2]



"[This] group of Scandinavian investigators raises concern of a potentially dangerous drug interaction with application of multimodal analgesia."

Multimodal approaches to perioperative pain are common in contemporary anesthesia practice. As posited by Kehlet and Dahl, "total or optimal pain relief cannot be achieved by a single drug or method or without significant side effects" and therefore they "recommend combined analgesic regimens (balanced analgesia) or a multimodal approach to the treatment of postoperative pain."[3] As they further explained, the "rationale for this strategy is achievement of sufficient analgesia due to additive or synergistic effects between different analgesics, with concomitant reduction of side effects, due to resulting lower doses of analgesics and differences in side-effect profiles." Since then, a plethora of primary studies, reviews, and meta-analyses have evaluated innumerable combinations of drugs and techniques for multimodal analgesia, and these are often enthusiastically and variably implemented throughout clinical practice.[4] American Society of Anesthesiologists Practice Guidelines for Acute Pain Management in the Perioperative Setting state that "whenever possible, anesthesiologists should use multimodal pain management therapy."[5]

The key question is how should practitioners assess all these drug combinations and the associated clinical studies and decide which combinations to implement clinically? One answer lies in evaluating the pharmacologic premise of combination therapies. Multimodal analgesia, conceptually and practically, rests almost exclusively on drug interactions that are pharmacodynamic (at the receptor or postreceptor level) not pharmacokinetic (changes in drug concentrations). Additivity occurs when the effect of two drugs together equals the sum of their individual effects, synergy occurs when the effect of two drugs together is greater than the sum of their effects when given alone, and potentiation occurs when one drug has no effect but increases the effect of another drug when given together.[6] The goal of multimodal pain therapy is additive analgesia, with subadditive or diminished toxicity, or, synergistic analgesia with only additive toxicity. Clinical studies evaluating such drug combinations should evaluate both analgesia and all the relevant side effects.

Gabapentin and pregabalin block α-2-δ calcium channels in neurons. Gabapentinoids alone can reduce pain and are approved by the Food and Drug Administration for postherpetic neuralgia, diabetic neuropathy, and fibromyalgia in adults. American Society of Anesthesiologists Guidelines recommend that gabapentinoids should be considered as part of a postoperative multimodal pain management regimen.[5] Oral gabapentinoids together with intravenous opioids may result in lower postoperative pain scores and reduced opioid consumption compared with intravenous opioids alone,[5,7,8] although the magnitude of these effects varies considerably among studies, and the dose and duration of treatment needed to obtain them remain unclear.[9] Reduction in nausea or vomiting by the combination is inconsistent.[5,7]

Image: A. Johnson.

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Pregabalin alone causes major side effects, most commonly in cognition and coordination, including confusion, dizziness, somnolence, ataxia, disturbed attention, and thinking abnormalities.[10,11] Pregabalin together with intravenous opioids causes greater postoperative side effects, including sedation, dizziness, visual disturbances, and confusion, than opioids alone.[7,8,12] Thus, numerous clinical studies have studied the combination of gabapentinoids and opioids, evaluating mainly analgesia (pain, opioid sparing), but less so, or often not, the relevant side effects.[12] Hence, the true value of multimodal opioid–gabapentinoid regimens remains incompletely established.

This issue of Anesthesiology reports the results of a clinical investigation by Myhre *et al.*[2] to address this very important issue. Their premise was that "to prove their utility in the perioperative period, the combination of opioids and gabapentinoids must demonstrate superior analgesia compared with either drug alone, and, furthermore, the combination should be beneficial compared with higher doses of opioid alone, and analgesic-related side effects should be reduced." They performed a clinical study in healthy volunteers, to examine the effects of remifentanil, pregabalin, and the combination, compared with placebo, on analgesia, ventilation, and cognitive function. The study used a crossover design, with each subject receiving all four treatments, and in randomized order, with enough time (washout) between treatment sessions to eliminate any carryover effects. Subjects received pregabalin (150 mg the night before and then again on the morning of the study day), a step-dose remifentanil infusion targeting increasing concentrations of 0.6, 1.2, and 2.4 ng/ml for 40 min each and/or placebo(s) (for each drug). On every study day, pain, ventilation, and cognition were each assessed four times. Pain was measured using the standardized cold pressor test, with subjects holding their hand in 3°C water for a maximum of 2 min and then rating their pain on a visual analog scale (0 to 100). Ventilatory function was evaluated by spirometry, measuring respiratory rate, minute volume, and end-tidal carbon dioxide, with end-tidal carbon dioxide being the main ventilatory parameter. Cognition tests measured executive functions and sustained attention.

The analgesia results were entirely consistent with previous observations, but the side effect data were somewhat surprising, and the juxtaposition of positive effects and side effects is provocative. Remifentanil alone caused dose-dependent analgesia, pregabalin alone caused mild analgesia, and the combination was *additive*. Remifentanil alone caused dose-dependent ventilatory depression (increased end-tidal carbon dioxide and decreased respiratory rate and minute volume), and pregabalin alone had no significant effect, but the combination caused greater ventilator depression than remifentanil alone; thus, pregabalin *potentiated* remifentanil ventilatory depression. Cognitive performance was significantly reduced by the combination of pregabalin and remifentanil but not consistently affected by either drug alone. These data in volunteers are consistent with a recent retrospective review that demonstrated an approximately 50% increased risk of respiratory events in the postanesthesia care unit in patients receiving more than 300 mg gabapentin preoperatively, a risk which was similar whether patients received general or neuraxial anesthesia.[13]

What are the clinical implications of the study by Myhre *et al.*? What is an acceptable incidence and magnitude of side effects to be paid for reduced pain and/or opioid consumption? An ideal multimodal drug combination causes greater analgesic effects and lesser side effects. In contrast, Myhre *et al.*[2] show that the combination of pregabalin and remifentanil caused *additive* analgesia but *potentiated* ventilatory depression and caused *greater* unwanted cognitive side effects (greater analgesia but greater side effects). It is conceivable that the analgesic effects of pregabalin alone and manner of interaction with remifentanil may differ in experimental nociceptive cold stimulation in healthy volunteers *versus* spontaneous and evoked neural activity occurring in patients sensitized after surgery. However, given ongoing concerns about postoperative ventilatory depression, particularly in the face of increasing prevalence of obstructive sleep apnea, as well as sedation, dizziness, and confusion, and the mixed picture of clinical effectiveness yet increased side effects when used in a multimodal regimen, available evidence to date suggests that the routine use of gabapentinoids in the perioperative period is yet not supported and perhaps not warranted. As in most questions of perioperative medicine, what we need are better data—what is the dose–response relationship of gabapentinoids for analgesia when combined with various opioids, and what is the relationship for adverse events from this combination, especially the risk of respiratory depression? The investigation by Myhre *et al.* is a great step in this direction.

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Competing Interests

Dr. Eisenach is the Editor-in-Chief of Anesthesiology, and his institution receives salary support from the American Society of Anesthesiologists (Schaumburg, Illinois) for this position. The other author declares no competing interests.

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Pregabalin Has Analgesic, Ventilatory, and Cognitive Effects in Combination with Remifentanil

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ABSTRACT

Background: Pregabalin is widely used perioperatively. The authors explored the effects of pregabalin, remifentanil, and their combination on experimental pain, ventilatory, and cognitive function.

Methods: In a randomized, double-blinded crossover study, 12 volunteers received (1) pregabalin + placebo, (2) placebo + remifentanil, (3) pregabalin + remifentanil, and (4) placebo + placebo. Pregabalin 150 mg/placebo was administered twice orally. After baseline, remifentanil/placebo was given as effect-site target-controlled infusion (TCI): 0.6, 1.2, and 2.4 ng/ml. Pain during cold pressor test was scored on visual analog scale (0 to 100 mm). Ventilation was measured by spirometry and cognition tested with Color-Word Interference and Rapid Information Processing tests.

Results: Pain intensity after placebo was (mean) 72 mm (95% CI, 62 to 83). Pregabalin reduced pain score by −10 mm (−14 to −7, $P < 0.001$). Remifentanil had dose-dependent analgesic effect, reducing pain score by −47 mm (−54 to −39, $P < 0.001$) on highest TCI level, whereas pregabalin + remifentanil exerted additive effect, reducing pain score by −57 mm (−64 to −50, $P < 0.001$). Respiratory depression was potentiated by adding pregabalin to remifentanil; end-tidal carbon dioxide was 39.3 mmHg (37.2 to 41.3) with placebo, increased 1.8 mmHg (−0.9 to 4.6, $P = 0.4$) with pregabalin, 10.1 mmHg (4.9 to 15.4, $P < 0.001$) with remifentanil, and 16.4 mmHg (11.3 to 21.5, $P < 0.001$) with pregabalin + remifentanil on highest TCI level. The combination pregabalin + remifentanil, but not either drug alone, adversely affected all cognitive tests.

Conclusions: The combination of pregabalin and remifentanil had additive analgesic effects, pregabalin potentiated remifentanil ventilatory depression, and the combination adversely affected cognition. These results question the clinical benefit of the combination compared with higher doses of opioids. **(ANESTHESIOLOGY 2016; 124:00-00)**

MULTIMODAL, balanced analgesia is used for the treatment of postoperative pain. The concept is based on a combination of drugs with different modes of action to achieve optimal pain relief and reduce opioid-related side effects such as nausea and sedation, which may have a substantial impact on patient recovery after surgery.[1,2]

During the past decade, gabapentin and its successor pregabalin have been introduced as potential analgesics for early and long-term pain after surgery.[3,4] Multiple studies have shown significant pain reduction and opioid-sparing effects in early postoperative pain[5–11]; however, the analgesic efficacy of these compounds for acute postoperative pain conditions remains controversial, as other studies did not confirm these positive findings.[12–15] A Cochrane review[16] concluded that there was no evidence of any beneficial effects of pregabalin in acute postoperative pain, whereas another systematic review[17] reported a reduced cumulative opioid consumption at 24 h postsurgery. Furthermore, two recent meta-analyses[18,19] concluded that pregabalin was associated with significantly reduced postoperative pain score both at rest and with movement, as well as significantly reduced opioid consumption at 24 h postsurgery compared with placebo.

What We Already Know about This Topic

- Pregabalin is commonly used in the perioperative period, but its interactions with opioids on sedation and ventilatory control are not well characterized

What This Article Tells Us That Is New

- In a crossover study in 12 volunteers not undergoing surgery, pregabalin, 150 mg twice a day, alone did not affect end-tidal carbon dioxide, but it mildly reduced pain report in a cold pressor test
- Pregabalin was additive with remifentanil for analgesia and potentiated respiratory depression from remifentanil
- The combination of these drugs adversely affected all cognitive tests, whereas each alone did not

Although gabapentin and pregabalin may have acute analgesic and antihyperalgesic properties in a postsurgical setting,[20,21] they are associated with undesirable side effects, such as sedation,[19] dizziness, visual disturbance,[22,23] and

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cognitive dysfunction.[24] In addition, a respiratory depressive effect of pregabalin has been proposed in one case series,[25] but no studies have examined this effect by using validated methods. To prove their utility in the perioperative period, the combination of opioids and gabapentinoids must demonstrate that the combination of the two drugs provides superior analgesia than either drug alone. Furthermore, the combination should be shown to be beneficial compared with higher doses of the opioid alone, and analgesic-related side effects should be reduced.

Drug combinations can most easily be studied in healthy volunteers. Validated methods for examining analgesia,[26] ventilation,[27] and cognitive function[28,29] exist and can be repeated within the same subject, thus increasing the statistical power.

The aim of this experimental crossover study in healthy volunteers was to examine the analgesic effect of pregabalin, the short-acting opioid remifentanil,[30] and their combination compared with placebo. Moreover, the study aimed at exploring the effects of pregabalin and remifentanil on ventilatory and cognitive functions.

Materials and Methods

The study was performed at Oslo University Hospital, Oslo, Norway, between November 2011 and February 2012. Approval was obtained from the Regional Committee for Medical Research Ethics for Eastern Norway, Oslo, and the Norwegian Medicines Agency, Oslo. The study is registered at ClinicalTrial.gov (NCT01419405, principal investigator: A.S.; June 30, 2011) and was reported in accordance with recommendations in the CONSORT 2010 Statement for randomized trials.[31]

The participants were recruited by an open invitation to students at the University of Oslo. Twelve healthy adults (equal numbers of males and females), American Society of Anesthesiologists classification I, age 23 yr (range, 20 to 28 yr), and weight 67 kg (range, 54 to 87 kg), participated in the study after written consent had been obtained. None of the participants had any known drug allergies or used any type of medication before or during the study. A history of alcohol or drug abuse was an exclusion criterion. All participants completed the study as planned, without dropouts or interfering medications.

This was a randomized, double-blind, placebo-controlled complete crossover study with four treatments: (1) pregabalin + remifentanil, (2) pregabalin + placebo, (3) placebo + remifentanil, and (4) placebo + placebo. Every participant received all four treatments in a randomized sequence, and each of the four treatments was administered on 4 different days. An investigator with no clinical involvement in the study prepared a computerized randomization list of the four treatment sequences A–D using block randomization. The block size was four or eight after randomization. The block size and randomization code were unknown to the investigators, and the treatment allocation was concealed in opaque, sealed, and sequentially numbered envelopes. The participants were assigned to the next consecutive participant number and provided with corresponding study medication. The randomization was not revealed to the investigators (M.M. and A.S.) before all measurements were conducted and entered into a database. To balance any possible period effects and carryover effects, a variance-balanced reduced Latin square design was used. This Latin square ensured that all subjects received all of the treatments, each treatment appeared an equal number of times in each period, and each treatment was followed by the same treatment an equal number of times.[32] Carryover effects were minimized by maintaining a consistent washout time of 72 h between two treatments, which corresponds to 11 times the elimination half-life ($t_{½}$ mean = 6.3 h)[33] of pregabalin, which was considered to be sufficient to ensure appropriate washout.[34]

Pregabalin 75-mg capsules and placebo capsules of identical appearance were produced by Oslo University Pharmacy, Oslo, Norway, and the capsules were prepacked in numbered and identical containers according to the randomization list and labeled with study information. Two nurses, who were not otherwise involved in the study, prepared 60-ml syringes of remifentanil 20 μg/ml (Ultiva®; GlaxoSmithKline, United Kingdom) or placebo (saline) immediately before administration and consistent with the treatment allocation. The prepared syringes had an identical appearance and were marked with the corresponding patient number and neutral study information.

Thirteen hours before the start of the trial, two capsules, each containing 75 mg of either pregabalin (a total of 150 mg) or placebo, were swallowed whole with a sip of water. The same dose of two capsules, each containing 75 mg of either pregabalin (a total of 150 mg) or placebo, was then repeated 1 h before the trial started. Food intake was restricted for 3 h before the start of the trial. By arrival, two IV cannulas were inserted, and an infusion of Ringer's acetate solution at a rate of 30 ml/h was started. Remifentanil or placebo was applied as a target-controlled infusion (TCI) (effect-site TCI, Minto model and Alaris® PK Syringe Pump; CareFusion, United Kingdom)[35] with increasing concentrations of 0.6, 1.2, and 2.4 ng/ml (TCI levels 1 to 3), with each level being maintained for approximately 40 min. This model takes into consideration the effect of age, sex, and lean body mass on pharmacokinetic parameters of remifentanil. To minimize the possible abrupt side effects such as hemodynamic instability, dizziness, or nausea and to reduce unblinding, the infusion rate was increased in a standardized stepwise manner over 2 min to reach the next level. During each study day, cognitive tests, ventilatory measurements, and experimental pain tests were performed four times. The first test was conducted approximately 1.5 h after the last oral medication but before the remifentanil/placebo infusion was started (level 0 = baseline), and then the tests were repeated at each TCI level 0.6 to 2.4 ng/ml (levels 1 to 3).

First, cognition was examined with tests designed to measure executive functions and the ability to sustained attention.

The Delis-Kaplan Executive Function System Color-Word Interference Test (CWIT)[28] is a test for inhibition and attention and consists of four parts: basic naming of color patches, basic reading of color words printed in black ink, inhibition of reading the words through naming dissonant ink colors in which those words are printed (Color-Word Interference), and switching between naming dissonant ink colors and reading the words (Color-Word Interference and switching). A total completion time and number of errors were calculated for all tests. The Rapid Visual Processing (RVP) test is a subtest from the Cambridge Neuropsycological Test Automated Battery (Cambridge Cognition, United Kingdom).[36] The test is measuring the ability to sustained attention and information processing. Two outcome variables were recorded: the RVP A' as a measure of sensitivity to the target based on the probability of correct hits and false alarms (0.00 to 1.00; bad to good) and the RVP mean latency defined as the mean time taken to respond within the response window of 1,800 ms.

Second, ventilatory function was measured by spirometry (Vmax Spectra 229®; SensorMedics Corp., USA). The device consisted of a facial mask, a mass flow sensor, and a nonrebreathing circuit with a low-resistance breathing valve. The mass flow sensor was calibrated daily and before every new participant with a 3-l syringe and against a standardized test gas (16% O_2 and 4% CO_2) according to the manufacturer's instructions. While sitting in a semiupright position with the facial mask carefully adjusted, the participants were requested to relax and breathe normally. Respiratory frequency, minute volume, and end-tidal carbon dioxide ($ETco_2$) tensions were automatically recorded. $ETco_2$ was used as main ventilatory parameter as this parameter is highly correlated to ventilation and all other ventilatory parameters. Furthermore, $ETco_2$ is mostly used in clinical practice. The participants were connected to the nonrebreathing circuit for approximately 10 min, and ventilatory data, considered representative from a 2-min period, were used for further analyses. For participant safety, peripheral capillary oxygen saturation was maintained above 90% by adding oxygen to the inhaled air. In cases of apnea periods greater than 15 s and significant oxygen desaturations to less than 92%, the participants were asked to take a deep breath, and additional oxygen was provided.

Finally, acute experimental pain was induced using a standardized cold pressor test (CPT). A refrigerated circulator (Julabo FP40-HE; Julabo Labortechnik GmbH, Germany) connected to a 13-l external custom-made Plexiglas (Evonik Industries AG, Germany) container was used providing a water temperature of 3.0° ± 0.01°C. The water temperature in the external container was calibrated with a precision thermometer, and the pump flow rate was 22 to 26 l/min. The subjects were asked to submerge their nondominant arm to the wrist into the water bath, holding the hand motionless and with fingers spread, for a maximum of 120 s. Pain was rated on a computerized visual analog scale (VAS) consisting of a vertical bar on a computer screen becoming red when the participants were scrolling the cursor with their dominant hand. The numeric value of the pain score, ranging from 0 mm (= no pain, lower anchor) to 100 mm (= unbearable pain, upper anchor), was hidden from the participants and was directly captured by the custom-made software. The pain score was reported every 10 s for a total of 12 times during each test, and the average of the last three values was used for further analysis. If a participant had to interrupt the CPT because of unbearable pain before the test was completed, the rest of the values were set to VAS = 100 mm. This was only the case in one of the subjects when treated with placebo + remifentanil (at TCI level 1) and placebo + placebo (at TCI levels 0, 1, 2, and 3).

At the end of each treatment, the participants were asked to specify side effects such as sedation, nausea, dizziness, pruritus, and headache. All test procedures were performed in the same manner at each level of remifentanil or placebo infusion. The cognitive tests started 10 min after change of TCI level, followed by spirometry, whereas CPTs started approximately 35 min after change in target level. Throughout the study, the participants were monitored with 3-lead electrocardiography, noninvasive blood pressure, and peripheral pulse oximetry. A written procedure describing how to handle adverse events, including a detailed list of rescue medications as well as predefined interruption criteria, was familiarized by all investigators.

The primary outcome was the mean of the three last VAS scores (0 to 100 mm) during the CPT. Secondary outcomes were the $ETco_2$ (mmHg), scores from cognitive tests, and side effects.

Statistical Analyses

The sample size was calculated using the software nQuery Advisor® Version 7.0 (Statistical Solutions, Ireland). We expected an average difference of 10 in pain intensity (VAS, 0 to 100 mm) between treatment groups. To compensate for six pairwise comparisons, the α level for the sample size calculation was set at 0.008 (Bonferroni correction). At least 12 subjects in total were required to demonstrate the difference with a power of 0.80 assuming an SD of 8.0 for the difference and no dropouts.

The mean and SD or median and ranges were given for normally and nonnormally distributed variables, respectively. Estimations of effect and differences between treatment group effects over infusion levels were examined using linear mixed random intercept models with pain intensity, ventilatory, and cognitive data as dependent variables. Treatment groups, infusion levels, and treatment-by-level interactions were defined as fixed effects, whereas subjects were treated as a random effect, and a compound symmetric correlation structure was assumed. A test for period effects was performed. The means and SDs from descriptive analysis were used to create figures 1–3. Two-sided *P* values corrected for multiple comparisons (Bonferroni adjusted) are presented. The significance level was set to 0.05.

Additivity of drug effects on analgesia was tested. For each individual subject, the differences between placebo and

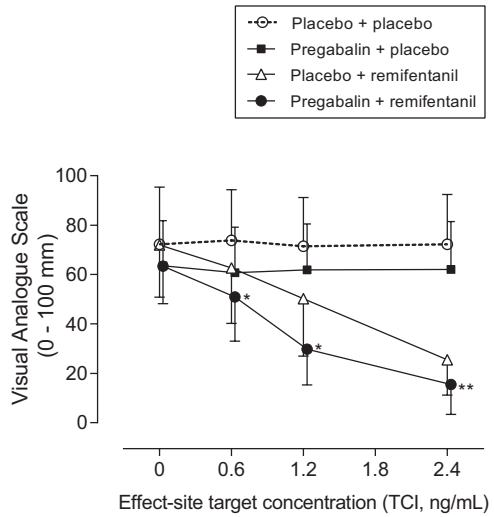

Fig. 1. Pain during cold pressor test at each target-controlled infusion (TCI) level. Data are presented as mean visual analog scale ± SD. Linear mixed random intercept model with Bonferroni correction for multiple comparisons was used to estimate the differences between treatment groups. Level of significance: $P < 0.05$. All treatments increased analgesia compared with placebo ($P < 0.001$). By pairwise comparisons at each TCI level 0.6 to 2.4 ng/ml (levels 1 to 3), pregabalin + remifentanil increased analgesia compared with placebo + remifentanil; −12 mm (−18 to −5, *$P < 0.001$) at level 1, −20 mm (−28 to −13, *$P < 0.001$) at level 2, and −10 mm (−17 to −3, **$P = 0.002$) at level 3.

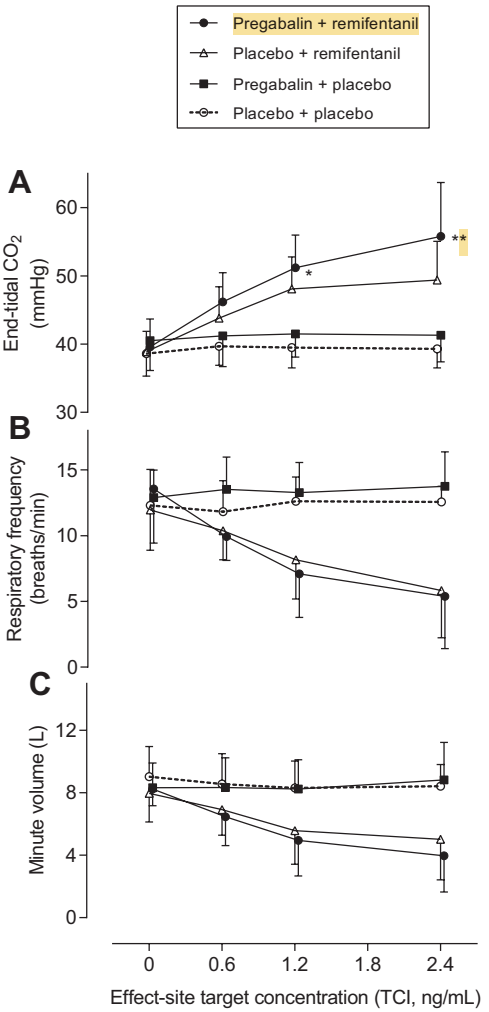

Fig. 2. (*A–C*) Ventilatory function expressed by (*A*) end-tidal carbon dioxide (mmHg), (*B*) respiratory frequency (breaths/min), and (*C*) minute volume (l/min) at each target-controlled infusion (TCI) level. Data are presented as means ± SD. Linear mixed random intercept model with Bonferroni correction for multiple comparisons was used to estimate the differences between treatment groups. Level of significance: $P < 0.05$. (*A*) End-tidal carbon dioxide (ET_{CO_2}) compared between active treatment groups and placebo at each TCI level 0.6 to 2.4 ng/ml (levels 1 to 3): pregabalin + placebo *versus* placebo ($P = 0.4$ to 1.0); placebo + remifentanil *versus* placebo ($P = 0.013$ to < 0.001); pregabalin + remifentanil *versus* placebo ($P < 0.001$). Pregabalin + remifentanil increased ET_{CO_2} compared with remifentanil alone; at level 2, *$P = 0.048$ and at level 3, **$P = 0.012$. (*B* and *C*) Respiratory frequency and minute volume were significantly reduced by placebo + remifentanil and pregabalin + remifentanil compared with placebo ($P < 0.001$). There were no significant differences between pregabalin + placebo *versus* placebo or pregabalin + remifentanil *versus* placebo + remifentanil.

each active treatment group (pregabalin, remifentanil, and the combination of pregabalin and remifentanil) were calculated. The sum of the calculated differences for pregabalin and remifentanil was then compared with the observed effect of the combination of pregabalin and remifentanil in a linear mixed random intercept model. Data analyses were performed with IBM SPSS Statistics 22 (SPSS Inc., USA).

Results

Pain intensity during the CPT (mean VAS ± SD) for all treatment groups and dose levels is displayed in figure 1. Mean pain intensity (mean VAS) was 72 mm (95% CI, 62 to 83) after placebo capsules and placebo infusion. In a linear mixed model analysis with pairwise comparisons with subjects as random intercept, pregabalin reduced pain score by mean −10 mm (−14 to −7, $P < 0.001$) compared with placebo. Remifentanil alone had a dose-dependent analgesic effect compared with placebo, reducing VAS score by −11 mm (−18 to −5, $P < 0.001$) at level 1, −21 mm (−28 to −14, $P < 0.001$) at level 2, and −47 mm (−54 to −39, $P < 0.001$) at level 3. Pregabalin in combination with remifentanil reduced VAS score by −22 mm (−29 to −16, $P < 0.001$) at level 1, −42 mm (−49 to −35, $P < 0.001$) at level 2, and −57 mm (−64 to −50, $P < 0.001$) at level 3 compared with placebo. By pairwise comparisons, the combination of pregabalin and remifentanil significantly increased the analgesic effect compared with remifentanil alone, showing additive analgesic effect of pregabalin (fig. 1). The analgesic effect of the combination at TCI levels 1 to 3 did not differ from the theoretical sum of the individual drug effects of pregabalin and remifentanil (combination − calculated sum; mean, −1 mm; 95% CI, −10 to 8, $P = 1.0$).

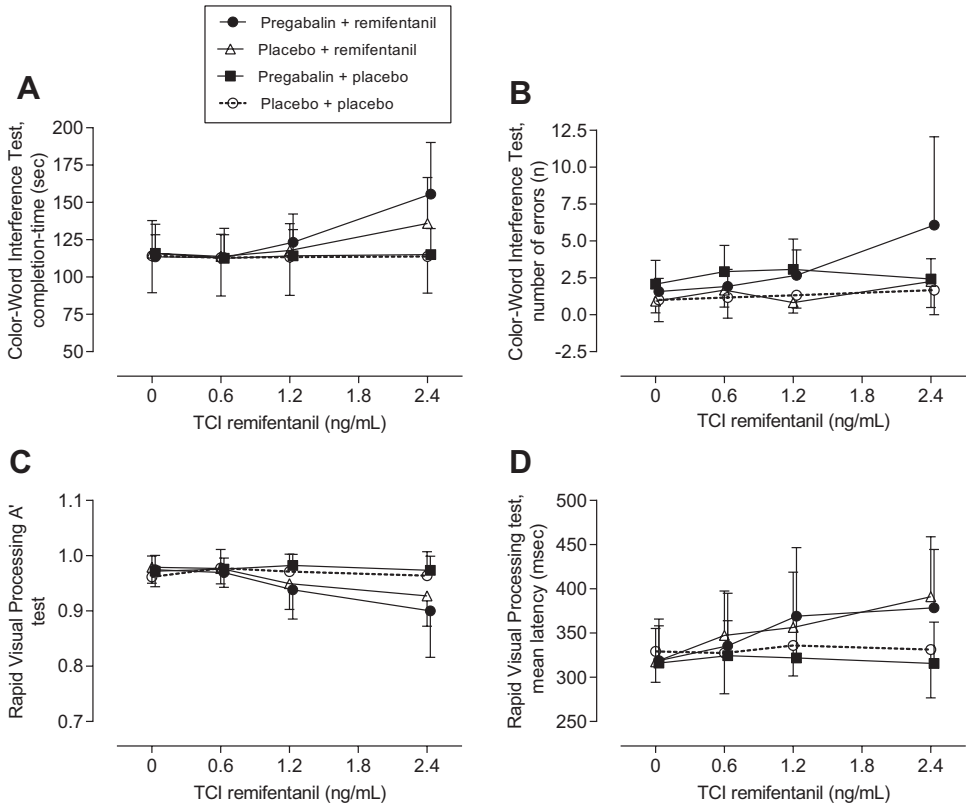

Fig. 3. (*A–D*) Cognitive function expressed by (*A*) Color-Word Interference Test (CWIT), completion time (seconds), (*B*) CWIT, number of errors (n), (*C*) Rapid Information Processing (RVP, A') test, and (*D*) RVP, mean latency (milliseconds). Data are presented as mean ± SD. Linear mixed random intercept model with Bonferroni correction for multiple comparisons was used to estimate the differences between treatment groups. By pairwise comparisons between treatment groups and placebo, pregabalin + remifentanil impaired all tests (*A–D*): *A*, $P < 0.001$; *B*, $P < 0.001$; *C*, $P = 0.003$; and *D*, $P = 0.028$. (*B*) Pregabalin + placebo increased CWIT, number of errors, $P = 0.004$; (*A*) placebo + remifentanil impaired the CWIT, completion time, $P = 0.029$; and (*C*) RVP, mean latency, $P = 0.009$. By pairwise comparisons between placebo + remifentanil and pregabalin + remifentanil, a significant increase in CWIT, number of errors was observed when pregabalin + remifentanil were administered (*B*), $P < 0.001$. TCI = target-controlled infusion.

Ventilatory effects were evaluated by $ETco_2$, respiratory frequency, and minute volume (fig. 2, A–C). Mean $ETco_2$ for placebo was 39.3 mmHg (95% CI, 37.2 to 41.3). Pregabalin alone did not change $ETco_2$ compared with placebo: 1.8 mmHg (−0.9 to 4.6, $P = 0.4$) at level 0, with minor changes on the other levels (fig. 2A). Remifentanil impaired all ventilatory parameters increasing $ETco_2$ by 4.1 mmHg (0.7 to 7.6, $P = 0.013$) at level 1, 8.6 mmHg (5.6 to 11.7, $P < 0.001$) at level 2, and 10.1 mmHg (4.9 to 15.4, $P < 0.001$) at level 3 compared with placebo. Pregabalin in combination with remifentanil increased $ETco_2$ by 6.6 mmHg (3.1 to 10.0, $P < 0.001$) at level 1, 11.7 mmHg (8.6 to 14.7, $P < 0.001$) at level 2, and 16.4 (11.3 to 21.5, $P < 0.001$) at level 3 compared with placebo. At level 3, this corresponds with a potentiation of the ventilatory depressant effect of remifentanil by 62% (95% CI, 10 to 113%; $P = 0.012$) caused by pregabalin.

Cognitive tests were evaluated based on the CWIT (completion time, number of errors) and RVP test (RVP mean latency, RVP A') (fig. 3, A–D). Pregabalin increased the number of errors in CWIT compared with placebo ($P = 0.004$), whereas remifentanil increased the completion time ($P = 0.029$) and the RVP mean latency ($P = 0.009$) compared with placebo. Pregabalin + remifentanil impaired all tests significantly compared with placebo (fig. 3, A–D). By pairwise comparison between pregabalin + remifentanil and placebo + remifentanil, there was no difference between the groups, except for increased number of errors when pregabalin + remifentanil was administered ($P < 0.001$).

The numbers of side effects in each treatment group are provided in table 1. In both groups receiving remifentanil, there were increased incidences of sedation, dizziness, and nausea compared with the placebo, and antiemetic drugs (metoclopramide and ondansetron) only had to be used when remifentanil was administered. When pregabalin was added to remifentanil, only minor differences were observed in the reported side effects compared with remifentanil alone. Pregabalin caused an increased number of side effects compared with placebo. Sedation and dizziness were reported in 75% of the cases in the pregabalin group compared with 42 and 25%, respectively, in the placebo group. There was no significant period effect between the treatments or visits ($P > 0.05$).

Table 1. Side Effects (n [%]) Reported by the Subjects during Each Treatment in the Crossover Study

	Placebo + Placebo	Pregabalin + Placebo	Placebo + Remifentanil	Pregabalin + Remifentanil
Subjects reporting side effects, n (%)	7 (58)	9 (75)	12 (100)	12 (100)
Total no. of side effects	14	28	47	49
Sedation, n (%)	5 (42)	9 (75)	12 (100)	12 (100)
Nausea, n (%)	2 (17)	3 (25)	9 (75)	10 (83)
Treatment of nausea, n (%)	0 (0)	0 (0)	2 (17)	3 (25)
Dizziness, n (%)	3 (25)	9 (75)	11 (92)	12 (100)
Pruritus, n (%)	0 (0)	1 (8)	6 (50)	7 (58)
Headache, n (%)	4 (33)	5 (42)	4 (33)	3 (25)
Diplopia, n (%)	0 (0)	1 (8)	5 (42)	5 (42)

Number of participants (n = 12).

Discussion

In this experimental placebo-controlled crossover study, we investigated the analgesic, ventilatory, and cognitive effects of pregabalin alone, remifentanil alone, and their combination. The main findings were significant additive analgesic effect and potentiated respiratory depressive effect when pregabalin and remifentanil were administered together. Furthermore, cognitive performance was significantly reduced by the combination of pregabalin and remifentanil, whereas inconsistent with either drug alone.

We chose to study the analgesic, ventilatory, and cognitive effects of pregabalin and remifentanil because the combination of opioids and pregabalin is of specific interest in the perioperative setting and has been implemented in several clinical protocols[37] although systematic reviews have shown conflicting results.[16,38] In this study, we found a small analgesic effect of pregabalin 150 mg × 2 compared with the placebo on acute cold pressor pain. Furthermore, when pregabalin and remifentanil were combined, the results showed additive analgesic effect with significant reduction in pain intensity on every TCI level compared with remifentanil alone. By adding pregabalin, comparable analgesia was achieved with an approximately 50% reduction in remifentanil dose, which can definitely be considered clinically significant.

In a previous study on cold pressor pain,[39] a single dose of 600 mg gabapentin combined with 60 mg oral morphine significantly increased the pain tolerance time with 76% compared with baseline, whereas morphine alone increased the pain tolerance time with 41%. Gabapentin alone did not increase the tolerance time significantly. The smaller analgesic effect of gabapentin alone compared with the significant effect of pregabalin alone in our study may be due to the different methods of pain assessment used. In the previous study, the CPT was evaluated by pain tolerance time. We assessed pain using the VAS,[40] which provides a continuous picture of pain intensity and is a sensitive method for evaluating pain.

The ventilatory effects were investigated in a non–steady-state model, measuring the effect of the drug on ET_{CO_2} and on ventilation, without external manipulation of the inhaled carbon dioxide concentration (closed-loop system).[27,41] Pregabalin alone did not change ET_{CO_2} significantly at any TCI level, whereas remifentanil had a dose-dependent ventilatory depressant effect. When pregabalin was added to remifentanil, the combination revealed a significant increase in ET_{CO_2} compared with remifentanil alone. At the highest TCI level (2.4 ng/ml), pregabalin + remifentanil increased the ventilatory depressant effect by 62% compared with remifentanil alone. These results show that pregabalin, similar to other sedatives such as propofol and benzodiazepines,[42,43] potentiates the ventilatory depressant effects of opioids.

In one clinical case series,[25] pregabalin was associated with respiratory depression in combination with opioids, and higher age, renal failure, and obstructive apnea syndrome were noted as relative contraindications for administering pregabalin in the perioperative setting. Our results show that the enhancement of the ventilatory depressant effect is present even in young, healthy subjects. A recent study[44] investigating pregabalin abuse in postmortem toxicology found that pregabalin was most commonly abused in combination with opioids. The authors suggested that profound central nervous system depression with possible respiratory failure could cause overdose-related deaths with pregabalin, particularly when coadministration with opioids occurred, thus indicating a potential interaction between opioids and pregabalin.

The cognitive tests were moderately affected by pregabalin, only increasing the number of errors in the CWIT, as a measure of impaired cognitive performance. The moderate effect of pregabalin alone on cognitive function in the current study is in accordance with comparable studies in healthy volunteers.[45] Remifentanil impaired the completion time (CWIT) and the mean latency (RVP) significantly, thus confirming results from earlier studies[46,47] indicating reduced psychomotor speed. However, the combination of pregabalin and remifentanil impaired all tests significantly compared with placebo and affected all cognitive tests numerically more extensively than each single drug alone. These effects on cognition may be of importance in the perioperative period, where delirium is a common risk factor for poor outcome, especially in elderly patients.[48]

Side effects were recorded after every treatment. Sedation and dizziness were more commonly reported when

pregabalin was administered compared with placebo, thus confirming findings from other clinical studies.[18,49] Remifentanil alone increased sedation, nausea, and dizziness significantly compared with placebo, whereas the combination of pregabalin and remifentanil only showed minor differences in side effects compared with remifentanil alone.

In this study, we chose to administer pregabalin 150 mg × 2 based on perioperative studies favoring 150 to 300 mg pregabalin daily.[50,51] A recent meta-analysis found consistent opioid-sparing effect with single doses of pregabalin from 75 or greater to 300 mg.[19] In addition, a Cochrane review reported high incidence of side effects (68%) and 4% serious adverse events after a single dose of 300 mg pregabalin.[16] Thus, our choice of 150 mg × 2 may be relevant for the perioperative period. In a study reported by Buvanendran *et al.*,[52] the maximum cerebrospinal fluid concentration of pregabalin was achieved as late as 8 h after an oral dose. We administered pregabalin 13.5 and 1.5 h before conducting the first CPT to optimize the drug concentration in the central nervous system. Such repeated dosing regimens is often used perioperatively.

Remifentanil, a strong and short-acting μ-agonist, was applied as opioid to achieve rapid onset of action and allowing for immediate changes between infusion levels.[30] The target concentration of remifentanil was set at TCI of 0.6 to 2.4 ng/ml. These concentrations are comparable to the steady-state infusion of 0.025 to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$[53] and have been shown to be relevant for early postoperative analgesia and superior to 10 to 20 mg IV morphine in the immediate postoperative setting.[54]

There are some limitations to this study. First, the study protocol did not include blood sampling and measurements of plasma drug concentrations. This means that, although unlikely,[55] a pharmacokinetic interaction between pregabalin and remifentanil cannot be ruled out. Second, we examined only one dose of pregabalin. Thus, no formal analysis of interaction between pregabalin and the opioid could be done, and our results cannot be extrapolated to other doses of pregabalin. Third, the ventilatory tests were conducted separately from the CPT and consequently not influenced by pain. Although this procedure allowed for perfect conditions to study the physiological effects of the drugs alone, it differs from the clinical reality, where patients are simultaneously influenced by both drugs and pain in addition to several other factors. Finally, the level of anxiety was not measured in our study, but anxiety may influence pain. Pregabalin has well-known effects in the treatment of general anxiety disorders[56] as well as in preoperative anxiety; hence, theoretically pregabalin may lead to lower pain scores due to an effect on anxiety. However, in a study investigating the effects of midazolam, an even stronger anxiolytic agent than pregabalin, doses up to 3 mg administered intravenously, did affect mood and psychomotor speed but not sensory and affective components of the cold pressor pain experience.[57] The same group found that midazolam did not enhance fentanyl analgesia in the same model.[58] This suggests that the severe CPT pain experience may be less affected by mood than other pain experiences and that the analgesia we observed after pregabalin is a pure analgesic effect not mediated by anxiolysis.

Taken together, our experimental human data show that the combination of pregabalin and the opioid remifentanil has additive analgesic effect. However, the results also reveal that pregabalin potentiates the ventilatory depressant effects of remifentanil and that the combination also affects cognitive function negatively. These results question the clinical benefit of the combination compared with higher doses of the opioid alone. Improved analgesia or reduced opioid consumption must be weighed against patient harms. Our findings raise serious concerns about the increasing use of pregabalin as an analgesic adjunct without strong evidence for improved recovery and overall patient benefit.

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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.

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