Original Investigation

Effect of Sedative Premedication on Patient Experience After General Anesthesia
A Randomized Clinical Trial

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IMPORTANCE Sedative premedication is widely administered before surgery, but little clinical evidence supports its use.

OBJECTIVE To assess the efficacy of sedative premedication on perioperative patient experience.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial, the PremedX study, enrolled 1062 adult patients who were younger than 70 years and had been scheduled for various elective surgeries under general anesthesia at 5 French teaching hospitals (in Marseille, Montpellier, Nimes, and Nice) between January 2013 and June 2014. Neurosurgery, obstetrical, cardiac, and outpatient surgery were excluded.

INTERVENTIONS Patients were randomized to 3 groups of 354 participants each to receive 2.5 mg of lorazepam, no premedication, or placebo.

MAIN OUTCOMES AND MEASURES The primary outcome was perioperative patient experience assessed 24 hours after surgery with a validated questionnaire (Evaluation du Vécu de l'Anesthésie Generale; EVAN-G) describing 6 domains of satisfaction and a global index (score range, 0-100; high scores represent high satisfaction); secondary outcomes included time to extubation and early cognitive recovery. A subgroup analysis was planned a priori in patients with a high level of preoperative anxiety.

RESULTS Premedication with lorazepam did not improve the EVAN-G mean global index for overall level of patient satisfaction (72 [95% CI, 70-73]; n = 330) compared with no premedication (73 [95% CI, 71-74]; n = 319) or placebo (71 [95% CI, 70-73]; n = 322) (P = .38). Among patients with heightened preoperative anxiety, there were no significant differences found in the EVAN-G mean global index between the lorazepam group (68 [95% CI, 65-72]; n = 87) and the no premedication group (73 [95% CI, 69-77]; n = 57) or the placebo group (70 [95% CI, 67-72]; n = 87) (P = .18). Time to extubation was 17 minutes (95% CI, 14-20 minutes) in the lorazepam group, 12 minutes (95% CI, 11-13 minutes) for the no premedication group, and 13 minutes (95% CI, 12-14 minutes) for the placebo group (P < .001) and the rate of early cognitive recovery was 51% (95% CI, 45%-56%), 71% (95% CI, 66%-76%), and 64% (95% CI, 59%-69%), respectively (P < .001).

CONCLUSIONS AND RELEVANCE Among patients undergoing elective surgery under general anesthesia, sedative premedication with lorazepam compared with placebo or no premedication did not improve the self-reported patient experience the day after surgery, but was associated with modestly prolonged time to extubation and a lower rate of early cognitive recovery. The findings suggest a lack of benefit with routine use of lorazepam as sedative premedication in patients undergoing general anesthesia.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01901003

JAMA. 2015;313(9):916-925. doi:10.1001/jama.2015.1108

Supplemental content at jama.com

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Patients scheduled for surgery may experience considerable stress, resulting in anxiety.[1] Benzodiazepine premedication is frequently used to reduce anxiety but also causes amnesia, drowsiness, and cognitive impairment,[2] which may be deleterious to some surgical patients.[3] Treating anxiety is not necessarily associated with a better perioperative experience for the patient.[4] Some patients may be concerned about their anxiety but others may not. Before antianxiety treatment is administered, patients should be provided the best information about its efficacy.[5] More needs to be known about the efficacy of preoperative anxiety treatment to better counsel patients to make informed decisions.

Patient satisfaction with the perioperative experience depends on a patient having experiences that match expectations.[6] To measure perioperative patient satisfaction, we developed and validated the Evaluation du Vécu de l'Anesthésie Generale (EVAN-G)[7] and the Evaluation du Vécu de l'Anesthésie LocoRégionale[8] scales that assess patient experience based on expectations for general and regional anesthesia, respectively. Undue anxiety can influence a patient's perioperative experience, which is why preoperative sedation is commonly given to surgical patients. To assess the efficacy of preoperative sedation in influencing a patient's perioperative experience, we performed a randomized clinical trial (the PremedX study) to compare the efficacy of lorazepam-based premedication with no premedication or a placebo.

Methods

Study Oversight

The multicenter PremedX study was funded by the French National Hospital Program of Clinical Research (Programme Hospitalier de Recherche Clinique). The study protocol and statistical plan were approved for all centers by the ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of Marseille University Hospital. The trial was monitored by an independent data and safety monitoring board.

Patients

Patients were enrolled between January 2013 and June 2014 at 5 French teaching hospitals (in Marseille, Montpellier, Nimes, and Nice) (more information appears in Supplement 1). All the departments of the 5 hospitals participating in this study belong to the Azurea Group research network. All consecutive patients scheduled for surgery were screened for study enrollment using the following eligibility criteria: adult patients younger than 70 years, weight of 45 kg or greater, elective surgery under general anesthesia, ability to complete a self-report questionnaire, and no contraindication to the use of benzodiazepines.

Exclusion criteria were neurosurgery; obstetric, cardiac, or outpatient surgery; patients specifically requesting anxiolytic premedication; pregnancy, respiratory failure, cognitive impairment, or drug abuse; and the use of neuroleptic medications or lithium. Patients receiving chronic benzodiazepine medications were allowed to continue their medications until the day before surgery.

Study Treatment

The lorazepam tablets contained 2.5 mg of the drug and were overencapsulated in No. 3-sized ivory capsules with microcrystalline cellulose added for volume. Placebo capsules contained only microcrystalline cellulose.

Treatment Protocol and Data Collection

All patients received written information about the study at the time of the anesthesiologist's consultation (at least 48 hours before hospital admission for surgery; more information appears in Supplement 2 and Supplement 3). This ensured that patients had sufficient time to learn about and understand the study protocol prior to granting consent to participate in the study. All participants provided written informed consent the day before surgery.

Patients were randomly assigned the day before surgery to receive lorazepam, no premedication, or placebo by a computerized program in random blocks of 2 patients per group at Timone Hospital. Patients filled out the Amsterdam Preoperative Anxiety and Information Scale (APAIS),[9] which is a validated instrument consisting of 6 items, to assess their preoperative anxiety level. The postoperative recovery of patients was assessed using the Postoperative Quality of Recovery Scale (PQRS),[10] which consists of the following 6 dimensions of recovery: cognitive, emotive, physiological, nociceptive, activities of daily living, and overall patient perspective (global index). The possible score range for the PQRS is from 0 to 100 and the results are expressed as the percentage of patients scored as recovered from the baseline assessment the day before surgery, 40 minutes after surgery, and on postoperative day 1 in accordance with intervals that were previously validated. We used the updated method of scoring for the cognitive assessment of the PQRS.[11]

Pain, quality of sleep, and well-being visual analog scales (VAS; score range, 0-100) were scored the day before and the day after surgery. Results were expressed as differences in VAS scores from baseline to adjust for interindividual variability across the broad array of surgical conditions.

Two hours prior to transferring the patient to the operating room, a nurse who was not involved in the study gave the allocated intervention. Patients allocated to the no premedication group did not receive any premedication and were informed of this by the nurse. Upon arrival in the operating room, the anesthetist (who was blinded to intervention assignment) evaluated the quality of patient cooperation using a VAS. Following this assessment, the anesthesiologist in charge could administer anxiolytic medication if he/she believed it was clinically necessary.

After surgery, the time to extubation was recorded and was defined as the interval between the end of hypnotic medication administration and withdrawal of the ventilation device (endotracheal tube or laryngeal mask). Anesthesia administration and airway management were delivered as per the anesthesiologist's usual practice and was not specified in the study protocol. Most anesthetists adhere to the French Society of Anesthesiology and Intensive Care Medi-

cine practice guidelines.[12] After surgery, patients were taken to the postanesthesia care unit (PACU). Upon arrival in the PACU, the pain and well-being VAS scores were obtained by PACU personnel. The PQRS was assessed at 40 minutes after surgery.

The day after surgery, patients were assessed with the EVAN-G questionnaire and the PQRS. The pain, quality of sleep, and well-being VAS were scored and compared with baseline values. The day after surgery, patients were asked to describe if they experienced any amnesia during the perioperative period and documented this at the bottom of the EVAN-G questionnaire. Comments made on the patient self-report form were reviewed by study personnel to assess amnesia. A modified Brice questionnaire to screen for intraoperative awareness was completed by the patients the day after surgery.[13]

Study Outcomes

Primary Outcome

The primary outcome was the EVAN-G[7] patient satisfaction global index evaluated on the day after surgery. The EVAN-G is a validated,[14,15] self-reported instrument that assesses patient experience and satisfaction during the perioperative period for general anesthesia.[16] The EVAN-G was developed from issues identified by patients to account for their concerns and experiences during the perioperative period.[17] A validation study prospectively enrolled 977 patients undergoing general anesthesia and demonstrated high reliability and validity.[7] A qualitative systematic review[16] of patient satisfaction measures noted a scarcity of well-developed satisfaction questionnaires and highlighted the robustness of the EVAN-G. The EVAN-G consists of 26 patient-generated items structured in 6 dimensions and a global index (score range, 0 [worst possible experience] to 100 [best possible experience]; eAppendix in Supplement 4). A score was obtained for each dimension by computing the mean of the item scores for the dimension. If less than half of the items were missing, the mean of the nonmissing items was computed as the score for the dimension (according to what was done in the validation study).

We planned an a priori subgroup analysis of preoperative anxiety as assessed by the APAIS for anxiety and used a cutoff of 11 to identify the most anxious patients.[18] The APAIS is a 6-item, self-reported questionnaire developed in a surgical population to evaluate the preoperative anxiety level of patients.[18] The items are scored on a 5-point Likert scale with responses ranging from "not at all" to "extremely." The APAIS score describes 3 different areas of preoperative anxiety: anxiety about anesthesia (A score), anxiety about surgery (S score), and a patient's desire to have information about the procedure. The anxiety score (range, 4-20) is the sum of the A score and the S score.[18] The APAIS has been translated into several languages,[9,19] and its usefulness was recently summarized.[20]

Secondary Outcomes

Secondary outcomes focused on the quality of patient cooperation, anxiety, pain, well-being, and quality of sleep. How well sedative premedication was tolerated was assessed by the rate of recovery (as measured by the PQRS); the time to extubation; and rates of hypothermia, shivering, sore throat, postoperative nausea, and vomiting. The hemodynamic and respiratory effects of anesthesia were evaluated 5 minutes after anesthetic induction. Hypotension was defined as a decrease of greater than 25% in systolic blood pressure from the value measured at the time of operating room arrival. Oxygen desaturation was defined as a pulse oximetry below 95% on pure oxygen inhalation. Tachycardia or bradycardia (ie, heart rate >120 beats/min or <50 beats/min) was also reported 5 minutes after anesthetic induction. The presence of a urinary catheter or gastric tube, ambulation, and resumption of eating within the first 24 hours were noted. Amnesia was determined by patient interview, intraoperative awareness by use of the modified Brice questionnaire, and postoperative complications by medical record review.

Statistical Analysis

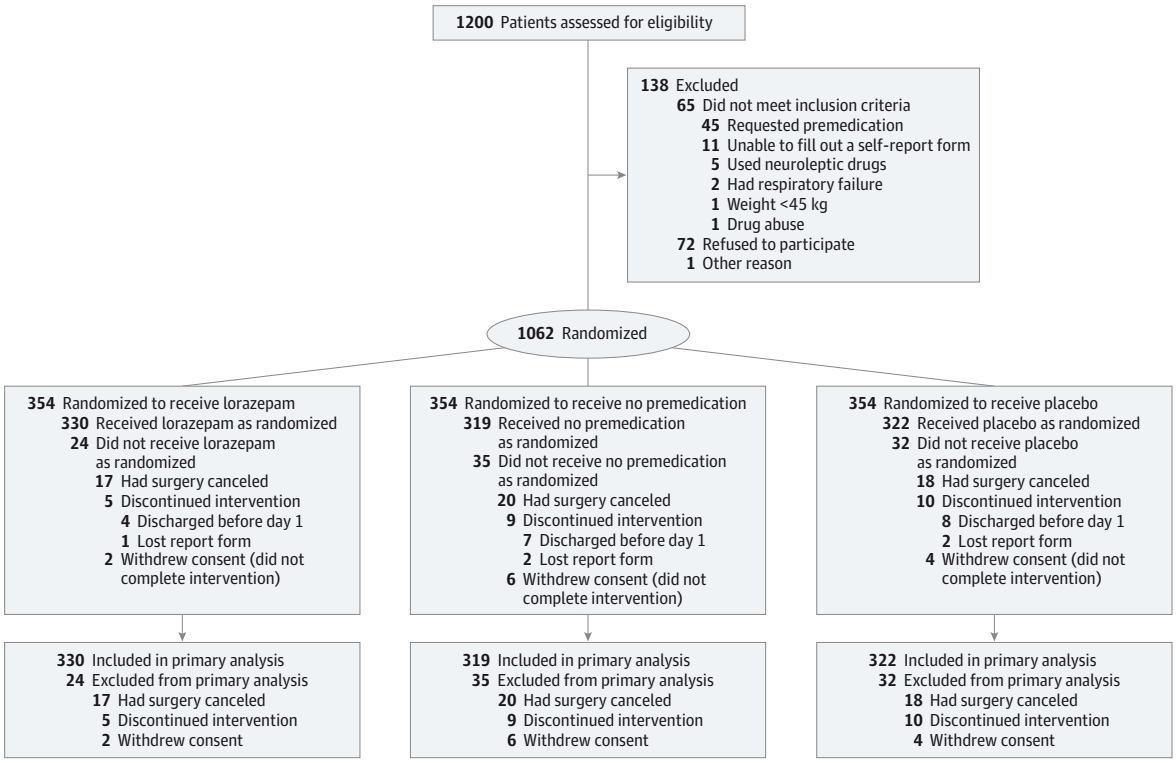
The sample size calculation was based on assumptions derived from our previous studies.[7,8] In the validation study population, the mean (SD) global index for the EVAN-G was 75 (14). An EVAN-G global index difference of 5 points was considered the minimum clinically important difference. For an α risk of 5% and power level of 80%, 969 patients were required with 323 patients in each of the 3 groups.[21]

All analyses were performed on an intention-to-treat basis for all end points. Patients who could not have an EVAN-G score calculated were excluded from the analysis. Statistical analyses were performed using SPSS Statistics version 20 (SPSS Inc). Data were expressed as mean and standard deviation or median and interquartile range. Differences between categorical variables were assessed by χ^2 analysis. Continuous variables were compared with 1-way analysis of variance. The Scheffe post hoc test was used to determine differences between individual variables if a global significant test result was present.

Because patient satisfaction could be influenced by several factors during the perioperative period, a multiple linear regression analysis also was performed. The dependent variables were the patient experience and satisfaction level as assessed by the EVAN-G. Explanatory variables for patient experience were entered into the model based on their clinical relevance. These variables included age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), American Society of Anesthesiologists physical status score, APAIS score, history of anxiety, depression, alcohol use, tobacco use, long-term treatment with a benzodiazepine or opioid, number of previous surgeries, and length of current surgery. An adjustment was made for multiple comparisons.

The *P* values were adjusted for each dimension and the global index for the whole population, as well as anxious (APAIS score for anxiety ≥11) and nonanxious patients (APAIS score for anxiety <11). Therefore, 21 *P* values were computed using a positive false discovery rate Q value, with the Spline method to adjust for multiple comparisons, using SAS version 9.2 with PROC MULTEST (SAS Institute Inc). A 2-sided *P* value of less than .05 was considered significant.

Figure 1. Flow of Patients in the PremedX Study



Results

A total of 1062 patients were randomized into the study between January 2013 and June 2014 (**Figure 1**). The baseline characteristics of the patients and types of procedures appear in **Table 1**.

Primary Outcome

For the EVAN-G mean global index, which measures overall patient satisfaction, no significant differences were found between the lorazepam group (72 [95% CI, 70-73]; n = 330) and the no premedication group (73 [95% CI, 71-74]; n = 319) or the placebo group (71 [95% CI, 70-73]; n = 322) (P = .38, **Table 2**). The differences remained nonsignificant in the multiple linear regression analysis after adjusting for confounding factors (P = .91). The model fit ranged from an R^2 of 0.03 to 0.24. Lorazepam was associated with a lower satisfaction score for the waiting dimension of the EVAN-G (assessing the patient experience of waiting time for the anesthetist and surgeon visits). In contrast, the pain dimension satisfaction score was higher in the lorazepam group than in the no premedication and placebo groups. The satisfaction scores for the attention, information, privacy, and discomfort dimensions were similar in all 3 groups (Table 2).

In a subgroup analysis of the most anxious patients (APAIS score for anxiety ≥11, n = 231), no significant differences were found in the EVAN-G mean global index between the lorazepam group (68 [95% CI, 65-72]; n = 87) and the no premedication group (73 [95% CI, 69-77]; n = 57) or the placebo group (70 [95% CI, 67-72]; n = 87) (P = .18, Table 2). In patients with an APAIS score for anxiety of 11 or greater, the mean (SD) global index for the EVAN-G was 70 (14); for those with an APAIS score for anxiety of less than 11, it was 73 (13) (P = .01).

For the attention dimension (assessed the attention patients received from caregivers during the perioperative period), lorazepam was associated with a lower satisfaction score than no premedication or placebo. For the pain dimension, the mean (SD) satisfaction score was 65 (23) in the lorazepam group (P = .77 for lorazepam vs no premedication), 68 (23) in the no premedication group, and 56 (24) in the placebo group (P = .05 for placebo vs no premedication; P = .01 for placebo vs lorazepam) ($F_{2,228}$ = 5.96; P = .003).

Secondary Outcomes

Quality of Recovery

Detailed reporting of the results for the secondary outcomes appears in **Table 3**. The time to extubation was significantly longer in the lorazepam group than in the no premedication and placebo groups. Forty minutes after the end of anesthesia, the rate of patients scoring as recovered in the PQRS cognitive dimension (n = 297) was significantly lower (χ^2_2 = 28.9, P < .001) in the lorazepam group (50.6%) than in the no premedication group (71.2%) and the placebo group (64.3%) (**Figure 2**). The rates of hypothermia, shivering, nausea, vomiting, and sore throat were similar in the 3 groups (Table 3).

On postoperative day 1, the number of patients with amnesia during the perioperative period was higher in the lorazepam group than in the no premedication group and the pla-

Table 1. Baseline Characteristics of Patients in the PremedX Study

	Lorazepam (n = 330)	No Premedication (n = 319)	Placebo (n = 322)
Age, mean (SD), y	49.7 (13.3)	50.5 (13.2)	48.7 (13.3)
Age group, No. (%)			
≤65 y	301 (91)	273 (86)	283 (88)
>65 y	29 (9)	46 (14)	39 (12)
Male sex, No. (%)	156 (47)	157 (49)	150 (47)
Body mass index, mean (SD)[a]	25.9 (4.9)	25.8 (5.3)	25.4 (5.1)
Weight status, No. (%)			
Under	7 (2)	10 (3)	13 (4)
Normal	150 (46)	147 (46)	155 (48)
Over	112 (34)	102 (32)	103 (32)
Obese	61 (18)	59 (19)	51 (16)
ASA physical status score, No. (%)			
1	171 (52)	158 (50)	170 (53)
2	118 (36)	120 (38)	121 (38)
3	33 (10)	37 (12)	25 (8)
4	7 (2)	4 (1)	6 (2)
No. of times received anesthesia previously, mean (SD)	3.8 (3.4)	4.0 (3.8)	3.7 (3.5)
History, No. (%)			
Anxiety	11 (3)	14 (4)	5 (2)
Depression	16 (5)	16 (5)	21 (7)
APAIS score, median (range)	8 (4-20)	7 (4-18)	7 (4-20)
Visual analog scale score, mean (SD)			
Well-being	67 (25)	71 (22)	68 (23)
Quality of sleep	59 (28)	61 (29)	61 (28)
Pain	29 (31)	28 (33)	29 (30)
Current or prior use, No. (%)			
Alcohol	21 (7)	28 (9)	25 (8)
Tobacco[b]	100 (30)	93 (29)	123 (38)
Benzodiazepine	48 (15)	41 (13)	36 (11)
Opioid	41 (12)	42 (13)	47 (15)
Type of surgery, No. (%)			
Orthopedic or spine	126 (38)	120 (38)	115 (36)
Digestive	43 (13)	60 (19)	44 (14)
Gynecologic	15 (5)	11 (3)	16 (5)
Vascular	7 (2)	2 (1)	5 (2)
Ear, nose, and throat	90 (27)	89 (28)	100 (31)
Maxillofacial	23 (7)	18 (6)	18 (6)
Thoracic	1 (<1)	0	0
Endocrine	25 (8)	19 (6)	24 (8)
Length of surgery, mean (SD), min	146 (68)	135 (61)	135 (63)
Surgery length <2 h, No. (%)	93 (28)	109 (34)	113 (35)

(continued)

cebo group. No significant difference was found between groups in regard to the PQRS rates for recovery, nausea, vomiting, and use of an anxiolytic or morphine.

Pain

Immediately after surgery, scores for the pain VAS were lower in the lorazepam group. This result was significant in the post hoc test, but only for lorazepam vs placebo (P = .001). This difference was no longer evident on postoperative day 1.

Patient Cooperation and Health-Related Perioperative Quality of Life

No difference was found between groups in the quality of patient cooperation upon arrival in the operating room. No significant difference was found in scores for the patient well-being VAS. There was no significant difference in the need for rescue premedication (Table 3).

The scores for the anxiety VAS were higher upon operating room arrival in the placebo group than in the no premedication and lorazepam groups. The rate of amnesia was associated with

the rate of missing answers ($P < .001$) on the EVAN-G (ie, items assessing the immediate postoperative period).

On postoperative day 1, variations in the scores for the well-being VAS from baseline were similar in the 3 groups. Quality of sleep improved significantly less in the lorazepam group compared with the no premedication and placebo groups. According to responses on the modified Brice questionnaire, 1 patient allocated to the placebo group was suspected of intraoperative awareness.

Anesthesia Tolerance and Cardiovascular Events

No difference was found between groups in the rate of hypotension, bradycardia, tachycardia, or oxygen desaturation 5 minutes after anesthesia induction (Table 3).

Table 1. Baseline Characteristics of Patients in the PremedX Study (continued)

	Lorazepam (n = 330)	No Premedication (n = 319)	Placebo (n = 322)
Type used, No. (%)			
Halogenated anesthetics	240 (73)	241 (76)	247 (77)
Etomidate	5 (2)	5 (2)	10 (3)
Propofol	317 (96)	308 (97)	307 (95)
Nitrogen oxide	46 (14)	43 (14)	51 (16)
Sufentanil	159 (48)	171 (54)	153 (48)
Remifentanil	159 (48)	137 (43)	148 (46)
Fentanil	0	1 (<1)	0
Alfentanil	1 (<1)	0	1 (<1)
Ketamine	28 (9)	30 (9)	34 (11)
Neuromuscular blocker	80 (24)	77 (24)	74 (23)
Perioperative warming	164 (50)	161 (51)	152 (47)
Adverse effects, No. (%)			
Difficult intubation	22 (7)	17 (5)	26 (8)
Perioperative incident	8 (2)	3 (1)	4 (1)

Abbreviations: APAIS, Amsterdam Preoperative Anxiety and Information Scale; ASA, American Society of Anesthesiologists.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] The only significant between-group difference ($P = .03$).

Table 2. Primary Outcome Comparisons for the PremedX Study

	EVAN-G Score, Mean (95% CI)[a]			*P* Value			*P* Value[c]	
	Lorazepam	No Premedication	Placebo	ANOVA	Adjusted ANOVA[b]	R^2	Lorazepamvs No Premedication	Lorazepam vs Placebo
Whole Population								
No. of patients	330	319	322					
Attention	74 (72-76)	77 (74-79)	75 (72-77)	.27	.12	0.03	.09	.77
Information	64 (61-66)	65 (63-67)	64 (62-67)	.54	.17	0.03	.74	.99
Privacy	67 (65-70)	68 (66-70)	66 (64-68)	.50	.17	0.04	.86	.17
Pain	68 (66-70)	66 (63-68)	63 (60-65)	.01	.02	0.10	.02	.001
Discomfort	83 (81-85)	81 (78-83)	81 (79-83)	.33	.14	0.09	.01	.21
Waiting	74 (71-77)	80 (77-83)	78 (75-81)	.01	.02	0.04	.01	.07
Global index[d]	72 (70-73)	73 (71-74)	71 (70-73)	.38	.15	0.07	.91	.30
Anxious Patients[e]								
No. of patients	87	57	87					
Attention	69 (64-74)	80 (76-85)	79 (75-83)	.001	.005	0.18	.007	.001
Information	60 (56-65)	66 (61-71)	62 (58-66)	.26	.12	0.08	.67	.71
Privacy	66 (62-70)	67 (62-73)	65 (61-69)	.79	.23	0.12	.79	.50
Pain	65 (60-69)	68 (62-74)	56 (51-61)	.003	.008	0.23	.77	.01
Discomfort	77 (73-82)	79 (75-84)	78 (75-82)	.83	.23	0.12	.90	.67
Waiting	73 (67-79)	76 (69-83)	80 (75-85)	.23	.12	0.13	.40	.02
Global index[d]	68 (65-72)	73 (69-77)	70 (67-72)	.18	.12	0.16	.39	.35

Abbreviations: ANOVA, analysis of variance; EVAN-G, Evaluation du Vécu de l'Anesthésie Generale.

[a] Unless otherwise indicated.

[b] Calculated using the Spline method with positive false discovery rate Q values.

[c] Calculated using a Scheffe post hoc test after multiple linear regression adjusted for age, sex, body mass index, American Society of Anesthesiologists physical status, history of anxiety, history of depression, alcohol use, tobacco use, long-term use of benzodiazepine, opioid usual treatment, number of previous surgeries, and length of current surgery.

[d] Indicates overall level of patient satisfaction.

[e] Defined as those having an Amsterdam Preoperative Anxiety and Information Scale score for anxiety of 11 or greater.

Table 3. Secondary Outcomes of the PremedX Study

	Lorazepam (n = 330)	No Premedication (n = 319)	Placebo (n = 322)	*P* Value for Lorazepam vs No Premedication	χ^2	*P* Value for Lorazepam vs Placebo
Operating Room Arrival						
Visual analog scale score, mean (95% CI)						
Quality of conditioning	76 (74 to 78)	74 (71 to 76)	73 (70 to 75)	.26		.09
Well-being	67 (64 to 69)	64 (61 to 67)	62 (59 to 65)	.38		.06
Anxiety	35 (32 to 38)	38 (35 to 41)	44 (40 to 47)	.41		.001
No. of venous puncture attempts prior to anesthesia induction, mean (95% CI)	1.21 (1.10 to 1.30)	1.13 (1.10 to 1.20)	1.14 (1.10 to 1.20)	.20		.29
Rescue premedication, No. (%)	2 (1)	3 (1)	6 (2)		0.29	
Anesthesia Tolerance and Cardiovascular Events						
Hypotension, No. (%)	108 (33)	126 (40)	122 (38)	.28		
Heart rate <50 or >120 beats/min, No. (%)	9 (3)	16 (5)	15 (5)		0.32	
Oxygen desaturation, No. (%)[a]	2 (1)	4 (1)	0		0.18	
Operating Room Departure						
Time to extubation, mean (95% CI), min	17 (14 to 20)	12 (11 to 13)	13 (12 to 14)	<.001		<.001
Visual analog scale score						
Pain	29 (37 to 32)	34 (31 to 37)	38 (34 to 41)	.09		.001
Well-being	56 (53 to 59)	56 (55 to 58)	56 (54 to 59)	.97		.99
Postanesthesia Care Unit Outcomes						
Total time, mean (95% CI), min	92 (83 to 102)	86 (80 to 92)	93 (87 to 98)	.53		.99
Temperature, mean (95% CI), °C						
At arrival	36.1 (36.0 to 36.2)	36.1 (36.0 to 36.2)	36.2 (36.0 to 36.2)	.57		.96
At departure	36.4 (36.3 to 36.5)	36.4 (36.3 to 36.5)	36.5 (36.4 to 36.5)	.93		.77
Nausea, No. (%)	26 (8)	25 (8)	33 (10)		0.15	
Vomiting, No. (%)	7 (2)	0	6 (2)		0.34	
Shivering, No. (%)	29 (9)	26 (8)	31 (10)		0.27	
Sore throat, No. (%)	112 (34)	114 (36)	127 (39)		0.17	
Received 1 local infiltration of surgical site, No. (%)	68 (21)	77 (24)	68 (21)		0.63	
Class II analgesics, No. (%)	205 (62)	218 (68)	219 (68)		0.23	
Morphine (patient-controlled analgesia), No. (%)	4 (1)	3 (1)	2 (1)		0.91	
Postoperative complications, No. (%)[b]	10 (3)	8 (3)	8 (2)		0.57	
Postoperative Day 1 Outcomes						
Amnesia, No. (%)	79 (24)	18 (6)	18 (6)	<.001		<.001
Change in visual analog scale score, mean (95% CI)[c]						
Pain	−8.0 (−11.8 to 4.3)	−6.6 (−10.7 to 2.6)	−7.8 (−11.7 to 3.9)	.88		.99
Quality of sleep	6.4 (2.5 to 10.3)	18.1 (13.9 to 22.3)	17.8 (13.6 to 22.0)	<.001		.001
Well-being	3.9 (0.5 to 7.3)	5.8 (2.7 to 8.9)	4.1 (0.9 to 7.4)	.72		.99
Anxiolytic use, No. (%)	12 (4)	14 (4)	12 (4)		0.37	
Nausea or vomiting, No. (%)	50 (15)	47 (15)	50 (16)		0.43	
Perambulation, No. (%)	270 (82)	268 (84)	269 (84)		0.35	
Eating, No. (%)	308 (93)	298 (93)	302 (94)		0.39	
Urinary catheter, No. (%)	29 (9)	21 (7)	23 (7)		0.43	
Gastric tube, No. (%)	2 (1)	5 (2)	2 (1)		0.15	
Morphine use, No. (%)	30 (9)	19 (6)	26 (8)		0.30	
Postoperative complications, No. (%)[b]	5 (2)	8 (3)	9 (3)		0.37	

[a] Defined as pulse oximetry below 95% on pure oxygen inhalation.

[b] Serious events according to the anesthetist in charge.

[c] Indicates variation between baseline and day 1.

Discussion

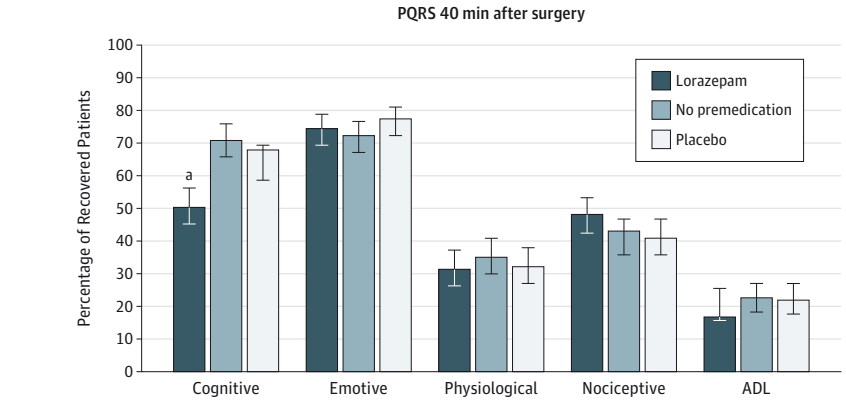
An important part of surgical outcomes is a patient's perception with the result of the intervention and overall experience in the perioperative setting. When assessing surgical outcomes, measuring patient satisfaction is necessary. A qualitative systematic review[16] of patient satisfaction measures noted a scarcity of well-developed satisfaction questionnaires and highlighted the robustness of the EVAN-G. Patient satisfaction should be measured by evaluation of the overall experience, which includes recovery from anesthesia, surgery, and pain, and improved health-related quality of life.[22] Anxiety, a potent behavioral and psychological reaction,[1] weighs heavily on a patient's perioperative experience and is exacerbated by preoperative concerns about underlying disease and impending anesthesia and surgery.[23,24]

To improve a patient's overall perioperative experience, anesthesiologists frequently administer preoperative anxiolytic medications to calm patients before they enter the operating room.[25,26] How well anxiety is treated by these medications and how they influence the overall perioperative experience is not known.

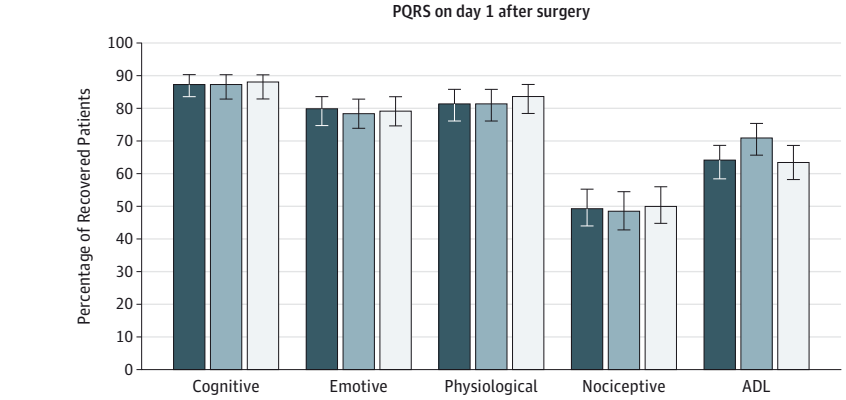
We performed the PremedX study to better understand the relationship between administration of preoperative anxiolytic medication and the overall patient experience. We found that preoperative sedation with lorazepam did not improve the perioperative experience or overall patient satisfaction. Compared with placebo, lorazepam did reduce patient anxiety upon arrival to the operating room. Because there was no overall benefit from preoperative anxiety treatment, it is possible that anxiety arising upon arrival to the operating room does not influence overall patient satisfaction.

In our study, 24% of patients displayed very high levels of preoperative anxiety. Previous studies have found similar proportions of patients experiencing a great deal of preoperative anxiety.[18] Because a minority of patients have high degrees of anxiety, there is little justification for routine administration of preoperative anxiolytic medication for all surgical patients. We did find in a subgroup analysis that anxiety experienced the day before surgery was associated with reduced

Figure 2. Recovery of Patients for Each Dimension on the Postoperative Quality of Recovery Scale (PQRS)



No. of recovered/total patients	Cognitive	Emotive	Physiological	Nociceptive	ADL
Lorazepam	160/316	228/306	84/266	147/306	53/316
No premedication	218/306	224/310	96/271	134/312	69/308
Placebo	196/305	241/312	92/287	128/312	68/310



No. of recovered/total patients	Cognitive	Emotive	Physiological	Nociceptive	ADL
Lorazepam	269/307	245/307	206/253	152/307	198/309
No premedication	259/297	233/296	200/246	144/296	210/296
Placebo	265/301	240/302	219/262	152/302	193/302

Error bars indicate 95% confidence intervals; ADL, activities of daily living.

[a] Comparisons between lorazepam and no premedication and placebo yielded a *P* value of less than .001.

overall perioperative patient satisfaction. Although exploratory, this finding suggests a potential benefit in the identification and treatment of anxiety the day before surgery. Prior studies showed a relationship between preoperative anxiety and the development of posttraumatic stress disorder, reinforcing the notion that patients prone to preoperative anxiety should receive specific attention.[27]

Preoperative sedation with lorazepam was associated with greater satisfaction with perioperative pain for all patients and less satisfaction with the attention received from caregivers among patients with high levels of preoperative anxiety. A study comparing intramuscular midazolam with placebo as preoperative sedation reported improved postoperative psychological and pain recovery.[28] The mechanisms on which these effects rely were unclear.

In our study, compared with placebo and no premedication, lorazepam was associated with more amnesia. The amnesia rate correlated with the number of missing answers on the EVAN-G items for assessing pain and attention. This could explain, in part, a higher pain domain satisfaction rating for the lorazepam group. Amnesia rates may also explain reduced satisfaction among anxious patients for the attention dimension. One interpretation of these results is that a patient's amnesia for pain is beneficial, whereas not remembering the attention provided by caregivers adversely affects the overall perioperative experience.

Our 3-group design revealed both placebo and nocebo effects in the perioperative setting. Pain scores were no different between the lorazepam and the no premedication groups but both groups had lower scores than the group given inert pills. This nocebo effect suggests that provision of inert pills can be harmful. Similarly, patients treated with placebo had higher anxiety scores upon arrival in the operating room than those in the no premedication group. The health psychology literature suggests that the nocebo response correlates with the level of anxiety,[29,30] and could be mediated by cholecystokinins.[31] In our study, placebo was accordingly associated with both elevated anxiety level and lower satisfaction score for the pain dimension. These results question the analgesic effect of sedative premedication because the placebo-controlled studies on which they rely could reflect a nocebo response.[32,33]

The quality of patient cooperation, the need for rescue premedication, the number of venous punctures, and the anesthesia protocol applied were similar in all 3 groups. Thus, patients who were premedicated with lorazepam were not necessarily easier to manage than patients in the placebo or no premedication groups. Lorazepam administration was associated with a prolonged time to extubation and decreased rate of cognitive recovery in the PACU. Prolonged recovery could limit the use of sedative premedication in patients receiving day-stay surgery.

The quality of sleep also was impaired in the lorazepam group. Worsening of sleep quality after lorazepam withdrawal was reported after a 7-day administration of the medication.[34] However, no study has evaluated this rebound phenomenon after the administration of a single dose. This finding could be of importance for early rehabilitation strategies in which sleep disturbances are recognized as perioperative risk factors.[35]

There were limitations to the PremedX study. A single drug and its placebo were tested. The design of the PremedX study aimed to test routine sedative benzodiazepine premedication, and its results probably represent a benzodiazepine class effect. We used lorazepam as the sedative premedication instead of midazolam. Midazolam has a shorter elimination half-life compared with lorazepam and diazepam. After an intravenous bolus for sedative premedication, midazolam has a greater effect on autonomic neurocardiac regulation than lorazepam and diazepam.[36] The choice of lorazepam was motivated by its use in the largest survey of sedative premedication published to date.[25]

Of the 3 randomization groups, 1 group included no premedication and these patients were aware they were not receiving any medication. Therefore, the lorazepam and placebo groups were double-blinded and the no premedication group was single-blinded. However, anesthesiologists, surgeons, and nurses were blinded to all 3 groups, and this approach to randomization and blinding revealed some interesting nocebo effects. The amount of anesthetic drugs administered was not collected but the sparing effect of benzodiazepine premedication has already been demonstrated[37]; however, this was not the object of the present study.

Conclusions

Among patients undergoing elective surgery under general anesthesia, sedative premedication with lorazepam compared with placebo or no premedication did not improve the self-reported patient experience the day after surgery, but was associated with modestly prolonged time to extubation and a lower rate of early cognitive recovery. The findings suggest a lack of benefit with routine use of lorazepam as sedative premedication in patients undergoing general anesthesia.

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Obtained funding: Maurice-Szamburski, Auquier, Bruder.
Administrative, technical, or material support: Maurice-Szamburski, Auquier, Viarre-Oreal, Cuvillon, Carles, Honore, Triglia, Leone, Bruder.
Study supervision: Maurice-Szamburski, Auquier, Bruder.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This work was supported by grant 2011-32 A-1337 from the French Institutional Clinical Hospital Research Program, Ministry of Health (awarded to Dr Maurice-Szamburski).

Role of the Funder/Sponsor: The French Institutional Clinical Hospital Research Program, Ministry of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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