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Continued midazolam versus diphenhydramine in difficult-to-sedate patients: a randomized double-blind trial

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Abstract

Background and Aims—Current guidelines recommend diphenhydramine in patients undergoing endoscopy who are not adequately sedated with a benzodiazepine and opioid combination. Because this practice has not been adequately assessed, we performed a randomized, double-blind trial comparing diphenhydramine to continued midazolam in such patients.

Methods—Patients undergoing elective colonoscopy with moderate sedation were eligible. Sedation was measured with the modified observer's assessment of alertness/sedation (MOAA/S) score with adequate sedation defined as 3 on a 0 to 5 scale. Patients not adequately sedated with midazolam 5 mg and fentanyl 100 mcg were randomly assigned to diphenhydramine 25 mg versus continued midazolam 1.5 mg. Adequacy of sedation was assessed 3 minutes after each study medication dose. If MOAA/S was 4 to 5, study medication was repeated, to a maximum of 3 doses. The primary endpoint was adequate sedation.

Results—The planned enrollment of 200 patients (100 in each study group) was attained. Adequate sedation was achieved less often with diphenhydramine than midazolam: 27% versus 65%, difference = −38%; 95% CI, −50% to −24%; p<0.0001. After study medications were completed, more patients required additional medication for sedation or analgesia with diphenhydramine versus midazolam (84% vs 68%, p=0.008), whereas the time to discharge from the recovery unit was similar (134 vs 129 minutes). Treatment effect was consistent across subgroups including age ≤55, substance abuse, benzodiazepine use, opioid use, and psychiatric medication use.

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Conclusions—Endoscopists performing moderate sedation should continue midazolam rather than switching to diphenhydramine in patients who do not achieve adequate sedation with usual doses of midazolam and an opioid.

INTRODUCTION

In the United States, sedation is integral to endoscopy and more than 98% of upper and lower endoscopies are performed with sedation[1]. The goal of sedation is to alleviate patient anxiety and pain and provide amnesia, thereby affording the patient and endoscopist with an optimal environment for a comprehensive examination. The consensus of U.S. GI societies is that moderate sedation is appropriate for average-risk patients undergoing upper endoscopy or colonoscopy[2,3].

Moderate sedation is generally performed using a benzodiazepine or a combination of a benzodiazepine and an opioid, with midazolam and fentanyl the most widely favored agents[3]. Guidelines indicate that the usual total dose of midazolam for endoscopic sedation is 2.5 to 5 mg[4]. However, some patients are not adequately sedated with the standard benzodiazepine and opioid combination, and in such patients current guidelines recommend the addition of diphenhydramine, as this “may allow adequate and safe sedation to be achieved”.[3]

BACKGROUND

No randomized trials have assessed the use of diphenhydramine in patients not adequately sedated with a benzodiazepine and opioid combination. Diphenhydramine hydrochloride, a histamine-1 receptor antagonist, is a central nervous system depressant that is widely used as a sedative agent for dental, ophthalmological and endoscopic procedures.[5–11]. Its onset of action is 2 to 3 minutes and its sedative effect lasts 240 minutes or more, which could potentially prolong recovery time compared with midazolam and fentanyl[5].

The goal of our study was to determine whether diphenhydramine is superior to continued use of midazolam in difficult-to-sedate patients who have not achieved adequate sedation with standard doses of midazolam and fentanyl.

METHODS

The study is an investigator-initiated, randomized, double-blind trial performed at the VA Connecticut Health Care System, between February 2013 and June 2015. The study was registered with ClinicalTrials.gov (NCT01769586) and approved by the institutional review board at the VA Connecticut Health Care System.

The randomization schedule was computer-generated by an individual uninvolved in the conduct of the study. The assignments were concealed using opaque coverings that were removed only at the time of randomization.

Population

Adults scheduled to undergo elective colonoscopy with moderate sedation were eligible. All eligible patients were approached consecutively for enrollment on days when 2 members of the study team could be present in the endoscopy suite. Patients were excluded if they had a documented allergy or adverse reaction to prior use of diphenhydramine, closed angle glaucoma, were unable or unwilling to provide informed consent, or were pregnant. Written informed consent was obtained from all participants who met eligibility criteria before the initiation of any sedation. Each patient received 2 L of supplemental oxygen via nasal cannula. The endoscopist-initiated sedation with midazolam and fentanyl at their discretion per routine practice up to a maximum of midazolam 5 mg and fentanyl 100 mcg. Patients were only randomized if they failed to achieve moderate sedation (assessed by study investigator as defined below) with 5mg midazolam and 100 mcg fentanyl.

Interventions

Patients were randomly assigned to receive intravenous diphenhydramine 25 mg versus midazolam 1.5 mg. Our rationale for using a total maximum dose of 75 mg of diphenhydramine comes from a study that demonstrated a dose of 75 mg was required to evoke a reproducibly robust sedative effect.[12] We chose a total maximum of 4.5 mg of midazolam based on another study showing that single doses of diazepam 10 mg (providing sedation comparable in potency to approximately 4.7 mg of midazolam) and diphenhydramine 75mg were approximately equal in sedative potency.[13] We concluded that diphenhydramine 25 mg and midazolam 1.5 mg should provide relatively comparable sedative potency and are commonly used doses for moderate sedation for endoscopy.

Three minutes after the first dose of study medication an investigator assessed the level of sedation (as described below). If patients were adequately sedated, the colonoscopy was started. If not, patients received another dose of their assigned study medication and sedation was again assessed 3 minutes later. This process was repeated for a maximum of 3 study doses.

If adequate sedation was achieved after the second or third study dose, the colonoscopy was begun. If adequate sedation was not achieved after the third study dose, the patient was considered to have failed to achieve adequate sedation. In such a scenario, the colonoscopy could be started or medications could be given at the discretion of the endoscopist. Additional medications for sedation and analgesia could be given during colonoscopy at the discretion of the endoscopist.

The patient, endoscopy personnel, and investigator assessing sedation were all blinded to the study medication. A separate individual, who was uninvolved in patient care or assessment, determined the randomization assignment, obtained the study medication (clear, colorless solutions in identical 5 mL syringes) in a separate room, and then administered the study medication.

Pulse rate and oxygen saturation were continuously monitored from the time sedation was initiated to discharge from the recovery room. Blood pressure was monitored at 5 minutes

until the end of the procedure, after which it was measured at 15-minute intervals, until discharge. Patients were also contacted by phone 24 hours after the procedure.

Outcomes

The primary endpoint was defined as success in achieving adequate sedation, assessed 3 minutes after the last dose of study medication was given and before initiation of the colonoscopy (as described above). Sedation was measured with the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale by a study investigator trained in this scoring system. This scale ranges from 0 to 5, where 0 denotes general anesthesia, in which the patient has no response to painful stimuli, and 5 denotes fully awake. MOAA/S was developed to measure the level of alertness in subjects who are sedated and is widely used in clinical research regarding sedation. Chernik et al[14] documented that the MOAA/S scale (the responsiveness score component of the OAA/S scale) is a reliable and valid instrument for measurement of the level of sedation.

The American Society of Anesthesiologists guidelines for sedation by a non-anesthesiologist define moderate sedation as a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation.[15] A score of 3 (patient responds after name called loudly or repeatedly) on the MOAA/S scale most closely matches this definition. Hence a score of 3 was used to define adequate moderate sedation.

Safety endpoints were (1) oxygen desaturation (<90% for ≥1 minute), (2) hypotension (systolic blood pressure <90 mm Hg), or (3) use of a reversal agent. Other endpoints included (1) time from first dose of study drug to discharge from recovery room; (2) need for additional sedation drugs after study drugs were administered (before or during colonoscopy); (3) post-procedural assessment of adequate procedural sedation by endoscopist; (4) post-procedural assessment of adequate procedural sedation by patient; and 5) patient willingness to repeat colonoscopy assessed 24 hours after the procedure. Endoscopists' and patients' assessment of adequate sedation were performed by asking if they felt adequate sedation was achieved (adequate vs inadequate). Patients were additionally contacted 24 hours later to determine if they would be willing to undergo a repeat colonoscopy with the same sedation medications (yes vs no).

Because use of adjunctive diphenhydramine is recommended in the difficult-to-sedate patients who fails to achieve adequate sedation with a standard benzodiazepine and opioid combination[3,5], we pre-defined variables for subgroup analysis that have been suggested to be predictive of difficult-to-sedate patients, including substance abuse (alcohol and drug), opioid use, benzodiazepine use, psychiatric drug use, younger age[5,16,17], and a composite of substance abuse and opioid, benzodiazepine and psychiatric medication use. Post-hoc multivariable analysis also was undertaken to determine the overall treatment effect of study medication for the primary endpoint when adjusting for these predefined variables.

Statistics

The hypothesis of this study was that diphenhydramine is superior in achieving adequate moderate sedation in difficult-to-sedate patients to the continued use of midazolam, based on

the guideline recommendation for use of diphenhydramine in patients not adequately sedated with the standard benzodiazepine and opioid combination. A paucity of data exists to provide estimates of the proportion of difficult-to-sedate patients who are adequately sedated with continued use of midazolam. Based on clinical experience, we posited that patients who continue to receive midazolam would achieve adequate sedation in 35% of cases. Hence a total of 192 patients were needed to show a 20% increase (from 35% to 55%) in the proportion of patients who achieve adequate sedation with diphenhydramine with α=0.05 and power of 80%. We planned on enrolling 200 total patients in a 1:1 ratio.

An intention-to-treat analysis was planned. Categorical variables were assessed using the Chi-square test. If fewer than 15 events occurred in either group, a Fischer's exact test was used to compare categorical variables. Continuous variables were compared using a 2-tailed Student t-test. Subgroup analyses were performed to identify qualitative interactions (treatment effects (ORs) for subgroups with and without the predefined characteristic in opposite directions: OR >1 and OR <1) and quantitative interactions (statistical heterogeneity ($p<0.05$) on interaction testing for treatment effects in subgroups using the Wald test). Post-hoc logistic regression analysis was undertaken to determine the treatment effect of study medication for the primary endpoint when adjusting for substance abuse, opioid use, benzodiazepine use, and psychiatric medication use.

RESULTS

Of 524 patients who met pre-endoscopic eligibility criteria, 324 were excluded because they achieved adequate sedation with midazolam 5mg and fentanyl 100mcg or less. The planned enrollment was achieved with 100 patients assigned to diphenhydramine and 100 to midazolam. All but 1 patient (in the midazolam group) received the intended treatment. Colonoscopy was unintentionally begun before administering the third study medication dose in this patient. Because the patient was not adequately sedated at the start of the colonoscopy, the individual was considered to have not achieved adequate sedation. All 200 patients were analyzed for the primary outcome (Figure 1).

Table 1 shows the baseline characteristics of all enrolled patients. Most patients were Caucasian males with an average age of 60. The groups were relatively comparable with somewhat more patients in the midazolam group taking opioids (23% vs 12%, p= 0.06) and somewhat more in the diphenhydramine group taking benzodiazepines (25% vs 15%, p= 0.11). Among those with substance abuse, 32 (32%) in the diphenhydramine group and 29 (29%) in the midazolam group had alcohol abuse.

Table 2 summarizes the results. The primary outcome, adequate sedation, was achieved less often with diphenhydramine than with midazolam (27% vs 65%, difference = −38%, 95% CI, −50% to −24%; $p<0.0001$). Only 1 dose of study drug was required more often with midazolam than diphenhydramine (33 [33%] vs 7 (7%), difference = 26%, 95% CI, 15%–36%). Potential sedation-related adverse events were relatively uncommon (Table 2), mild, and transient, with no reversal agents or other interventions required and no clinical sequelae.

After the doses of study medication were completed, more patients who received diphenhydramine required additional medication for sedation or analgesia (before the colonoscopy was initiated and/or while the procedure was being performed) than those who received midazolam: 84% versus 68%, p=0.008. The mean total doses of midazolam and fentanyl (including study doses of midazolam) given after randomization were 1.6 mg and 62.8 mcg in the diphenhydramine group and 4.2 mg (including study doses of 3.2 mg) and 38.0 mcg in the midazolam group; the mean doses given during the colonoscopy were 1.1 mg and 41.8 mcg in the diphenhydramine group and 0.8 mg and 27.8 mcg in the midazolam group. No significant differences were found in the mean times from first dose of study drug to discharge from the recovery room or colonoscopy completion rates (Table 2). Postprocedural assessment of adequacy of sedation and willingness to repeat colonoscopy were not obtained from 7% and 8% of patients, and 3% of endoscopists did not provide assessment of sedation adequacy, but no significant differences were identified in these outcomes (Table 2).

Subgroup analyses are shown in Table 3. No qualitative interaction was seen: the treatment effect was qualitatively consistent across subgroups with fewer patients achieving adequate sedation with diphenhydramine than midazolam (ORs<1) in all subgroups. In addition, no quantitative interaction was identified for any subgroup: p-values were >0.05 on interaction tests. Treatment effects were also similar in those with (OR=0.24, 0.08–0.70) and without alcohol abuse (OR=0.18, 0.09–0.38). The multivariable regression model that adjusted for age, substance abuse, opioid use, benzodiazepine use and psychiatric medication use confirmed that diphenhydramine was independently associated with a reduced odds of adequate sedation: OR=0.20; 95% CI, 0.10 to 0.37. Pre-endoscopic use of benzodiazepines was also independently associated with reduced odds of achieving adequate sedation in the multivariable analysis (OR=0.26, 0.10–0.65), but significant associations were not seen for substance abuse, opioid use, or psychiatric medication use.

DISCUSSION

Current American Society for Gastrointestinal Endoscopy guidelines provide a strong recommendation for the use of diphenhydramine as an option in patients who are not adequately sedated with a benzodiazepine and opioid combination[3], and, anecdotally, endoscopists often use diphenhydramine in patients who are difficult to sedate or are expected to be difficult to sedate. However, no prior randomized trial has assessed the efficacy of diphenhydramine in patients not adequately sedated with a standard moderate sedation regimen.

Based on the current guidelines and anecdotal opinions, we performed a randomized double-blind trial with the hypothesis that diphenhydramine would be more effective at achieving sedation than continued midazolam in patients who are not adequately sedated with midazolam 5 mg and fentanyl 100 mcg. Contrary to our hypothesis, we did not found that diphenhydramine was superior. In fact, continued midazolam was markedly superior to diphenhydramine in this population, with more than twice as many patients achieving adequate sedation. More patients assigned to diphenhydramine also required additional medication for sedation or analgesia, but other secondary endpoints, including post-

procedural physician and patient assessment of sedation, time until discharge, and willingness to repeat the procedure were similar in the 2 groups. Adverse events were infrequent, mild, and not significantly different between the treatment groups.

The similarities between the 2 groups in postprocedural physician and patient assessments of sedation cannot be taken to suggest comparable efficacy of diphenhydramine vs. continued midazolam. After the study medications were given, additional medications could be administered as needed before and during the procedure to ensure patients were comfortable. In a blinded study, similar results in the 2 study groups would be expected in the post-procedural assessment of sedation because endoscopists should be attempting to achieve adequate sedation during the procedure in all patients. Importantly, significantly more patients in the diphenhydramine group than in the midazolam group required additional medication for sedation or analgesia to achieve similar proportions in the 2 groups with adequate sedation reported pos-procedure.

The main limitation of our study is the fact it was performed exclusively in veterans with over 90% of participants male. The results therefore may not be generalizable to other populations, such as women, and a randomized trial in a more general population would be useful to assess the generalizability of our findings. Only about a quarter of patients were less than 55 years of age, but we found no suggestion of a difference in treatment effect between those aged 55 years or less and those above 55 years old. Nearly two-thirds of the patients had reported substance abuse or used opioids, benzodiazepines, or psychiatric medications. Although such patients may not be representative of a routine colonoscopy population, they may be more representative of patients in whom adequate sedation is not achieved with routine doses of midazolam and fentanyl and patients in whom endoscopists often add diphenhydramine based on anecdotal experience. The treatment effect remained consistent across all subgroups: ie, diphenhydramine was less effective than continued midazolam in patients with substance abuse or those who used opioids, benzodiazepines, or psychiatric medications. As might be expected, use of benzodiazepines was associated with a decreased chance of adequate sedation regardless of the sedation used.

Although the onset of action of diphenhydramine (2–3 minutes) is slightly slower than midazolam (1–2 minutes)[5], our protocol provided sufficient time to ensure assessment of the sedative effect of diphenhydramine. The usual dose of intravenous diphenhydramine used as an adjunct for endoscopic sedation is 25 to 50 mg[5]. A finding of inadequate sedation in our study was not made until at least 6 minutes after the standard 50 mg of diphenhydramine had been administered and 3 minutes after 75 mg had been given. Furthermore, the difference between groups continued well after the study medications were given: after the doses of study medication were completed, additional medications for sedation or analgesia were required significantly more often throughout the procedure in those given diphenhydramine than in those given midazolam.

As mentioned, no previous randomized trial has assessed the use of diphenhydramine in patients not achieving adequate sedation with standard moderate sedation medications. Tu et al[18] performed a double-blind randomized trial in patients undergoing colonoscopy, comparing 50 mg of intravenous diphenhydramine versus placebo given 3 minutes before

starting sedation with midazolam and meperidine. Endoscopists gave incremental doses of midazolam and meperidine until they judged sedation to be adequate. The primary outcome, based on the authors' sample size determination, was meperidine dose. As expected, the doses of meperidine and midazolam were significantly lower in the diphenhydramine arm, although the total cost for medication was significantly higher. Sedation was scored on a non-validated 1 to 10 point scale. Diphenhydramine was associated with 0.4 and 0.7 higher sedation scores for patients and attending endoscopists, values that are unlikely to be at or above a minimal clinically important difference. Qualitative assessments of sedation were comparable in the study groups as were times and adverse events. Although this prior study suggests that diphenhydramine is an acceptable adjunct when starting moderate sedation, it does not address the question of whether diphenhydramine is useful in patients not adequately sedated with a benzodiazepine plus opioid.

Diphenhydramine may be administered in different ways in clinical practice. Some endoscopists give diphenhydramine before or with the first dose of midazolam and an opioid agent, as done by Tu et al[18]. Others may add it to midazolam and fentanyl in patients who appear to have little effect after their initial doses of midazolam and fentanyl. In contrast, current guidelines recommend administration of diphenhydramine when standard doses of midazolam and an opioid agent don't provide adequate sedation[3], and we designed our trial to assess this guideline recommendation. Our results cannot be generalized to the other dosing schedules of diphenhydramine that may be used in clinical practice.

We confined our study to patients undergoing colonoscopy, the most common gastrointestinal endoscopic procedure performed in the United States.[19] Our results may not be generalizable to other types of procedures, whether shorter and less complex (eg, upper endoscopy) or longer and more complex (eg, endoscopic retrograde cholangiopancreatography). For example, different results in outcomes such as time to discharge might be identified in a shorter duration procedure such as upper endoscopy. Separate studies in different types of procedures are necessary to evaluate sedation in these settings

In conclusion, endoscopists should continue midazolam rather than switching to diphenhydramine in patients who do not achieve adequate sedation with usual doses of midazolam and an opioid. Guidelines should be updated to reflect this new evidence. Further research to identify other potentially safe and well-tolerated medications that could be used in the "difficult-to-sedate" patient is warranted.

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ACRONYMS

MOAA/S Modified observer's assessment of alertness/sedation

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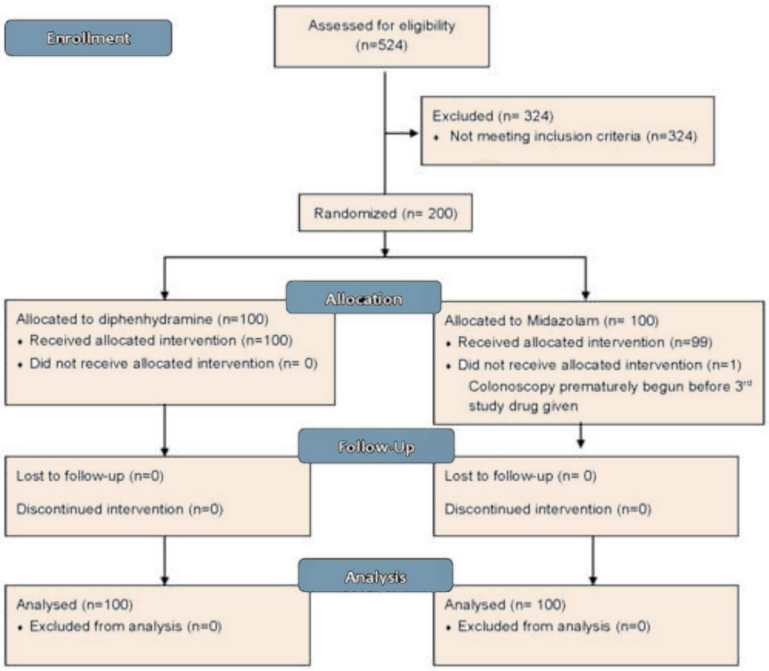

Figure 1.
Flow Diagram of Study

Table 1

Selected baseline characteristics of study groups

	Diphenhydramine (N=100)	Midazolam (N=100)	P value
Male	94	93	1
Age, mean ± SE (yrs)	60 ± 1	61 ± 1	0.37
Age < 55 yrs	24	23	1
Body mass index, mean ± SE (kg/m^2)	31 ± 1	31.4 ± 1	0.50
White	88	82	0.32
African-American	9	16	0.20
Hispanic	3	2	1
Substance abuse	34	34	1
Opioid use	12	23	0.06
Benzodiazepine use	25	15	0.11
Psychiatric medication use	32	36	0.65
Screening colonoscopy	50	51	1
Surveillance colonoscopy	36	39	0.77
Diagnostic colonoscopy	14	10	0.51

Table 2

Results for pre-defined endpoints

	Diphenhydramine (N=100)	Midazolam (N=100)	Difference (95% CI)
Adequate sedation	27 (27%)	65 (65%)	−38% (−50% to −24%)
Oxygen saturation <90% for ≥1 minute	1 (1%)	2 (2%)	−1% (−6% to 4%)
Systolic blood pressure <90mm Hg	1 (1%)	6 (6%)	−5% (−12% to 0.5%)
Use of reversal agent	0 (0%)	0 (0%)	0% (−4% to 4%)
Additional sedation drugs given after study drug	84 (84%)	68 (68%)	16% (4% to 27%)
Colonoscopy completed	96 (96%)	96 (96%)	0% (−6% to 6%)
Endoscopist post-procedural assessment: adequate procedural sedation	81/96 (84%)	83/98 (85%)	−0.3% (−11% to 10%)
Patient post-procedural assessment: adequate procedural sedation	90/94 (96%)	84/92 (91%)	4% (−3% to 12%)
Patient willing to repeat (24-hr assessment)	83/93 (89%)	86/92 (93%)	−4% (−13% to 4%)
Time from first dose of study drug to discharge from recovery (mean± SE)	134 min ± 3	129 min ± 4	6 min (−3 min to 15 min)

Table 3

Subgroup analyses comparing treatment effect (odds ratio for adequate sedation with diphenhydramine vs. midazolam) in subjects with and without predefined baseline characteristics

	Diphenhydramine	Midazolam	OR (95% CI)
Age ≤55 years	6/24 (25%)	16/23 (70%)	0.15 (0.04–0.53)
Age >55 years	21/76 (28%)	49/77 (64%)	0.22 (0.11–0.43)
Substance abuse	10/34 (29%)	23/34 (68%)	0.20 (0.07–0.56)
No substance abuse	17/66 (26%)	42/66 (64%)	0.20 (0.09–0.42)
Opioid use	4/12 (33%)	10/23 (43%)	0.65 (0.15–2.79)
No opioid use	23/88 (26%)	55/77 (71%)	0.14 (0.07–0.28)
Benzodiazepine use	4/25 (16%)	5/15 (33%)	0.38 (0.08–1.73)
No benzodiazepine use	23/75 (31%)	60/85 (71%)	0.18 (0.09–0.36)
Psychiatric med use	8/32 (25%)	25/36 (69%)	0.13 (0.04–0.38)
No psychiatric med use	19/68 (28%)	40/64 (63%)	0.25 (0.12–0.52)
Substance abuse; opioid, benzodiazepine, or psychiatric med use	17/65 (26%)	42/63 (67%)	0.18 (0.08–0.38)
No substance abuse; opioid, benzodiazepine, or psychiatric med use	10/35 (29%)	23/37 (62%)	0.24 (0.09–0.66)