# Use of diphenhydramine as an adjunctive sedative for colonoscopy in patients on chronic opioid therapy: a randomized controlled trial CME

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**Background and Aims:** Chronic opioid use increases tolerance to sedatives. Diphenhydramine is recommended for difficult-to-sedate patients during endoscopic procedures. We hypothesized that the addition of diphenhydramine to midazolam and fentanyl would improve objective and subjective measures of procedural sedation.

**Methods:** This randomized, double-blind, placebo-controlled trial included patients on chronic opioids undergoing colonoscopy. Patients were randomized to receive 50 mg of diphenhydramine intravenously (n = 61) or placebo (n = 58), in addition to fentanyl and midazolam. Baseline characteristics, amount of fentanyl and midazolam, procedure times, and adverse events were recorded. Quality of sedation was assessed by the physician and nurse. Patients rated pain and amnesia on a 10-point scale.

**Results:** There was no difference in amounts of fentanyl (125.4 ± 56.2 μg vs 126.9 ± 53.5 μg, $P$ = .88) and midazolam (4.9 ± 2.1 mg vs 5 ± 1.9 mg, $P$ = .79) used. The mean sedation scores from the physician (6.2 ± 1.1 vs 5.3 ± 1.2, $P$ = .0002) and nurses (5.6 ± 1.5 vs 5.1 ± 1.4, $P$ = .04) were statistically significant in favor of the diphenhydramine arm. Patient scores for pain (2.05 ± 2.17 vs 3.09 ± 3.95, $P$ = .047) and amnesia (7.8 ± 3.4 vs 6.5 ± 3.8, $P$ = .047) favored the group that received diphenhydramine. Qualitative assessment showed no significant difference between the groups. There was no difference in induction time ($P$ = .86), procedure duration ($P$ = .98), or recovery time ($P$ = .16). Hypotensive episodes were more common in the placebo group ($P$ = .027).

**Conclusions:** In patients on chronic opioid therapy, administration of diphenhydramine does not allow for lower doses of procedural sedatives but improves quality of sedation without increasing the number of adverse events. (Clinical trial registration number: NCT T01967433.) (Gastrointest Endosc 2018;88:695-702.)

## INTRODUCTION

Patient comfort is important for successful and safe completion of colonoscopy, and results in increased compliance and willingness to undergo repeat procedures.[1,2] At times, adequate sedation cannot be achieved. This results in patient discomfort, unsatisfactory examination, incomplete procedures, wasted time, and financial loss.[3-8] Although results are conflicting, factors that predict difficult sedation include excessive alcohol use (>40 g/day), psychotropic medication, opioid use, and anxiety.[9,10]

*Abbreviations: IQR, interquartile range; SD, standard deviation; VAMC, Veterans' Affairs Medical Center.*

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There has been a dramatic increase in the use of opioid pain medications in the last few decades.[11,12] According to estimates, more than 238 million prescriptions were written for narcotic analgesics during 2011.[11] The increasing use of opioids in the general population and the associated cross-tolerance with conventional sedatives can lead to an increased dose requirement for sedatives used during endoscopic procedures. In addition, chronic opioid use has been linked to opioid-induced hyperalgesia, which can increase pain and discomfort during endoscopic procedures, further increasing the dose of sedatives required.[1,13]

Our recent evaluation of outpatient colonoscopies showed that, despite receiving significantly higher doses of fentanyl and midazolam for sedation, patients on chronic opioids were more likely to report pain.[8] The higher dose of fentanyl and midazolam required to achieve adequate sedation is concerning, given the associated risks of respiratory depression and hypotension.[13,14] Based on anecdotal data, adjunct sedatives and deeper sedation with propofol are often used in this unique patient population.[15,16] Because of its depressant effects on the central nervous system, diphenhydramine hydrochloride has been explored as an adjunct to meperidine and midazolam and has shown promise in the general population.[17,18] However, no study has specifically examined the use of diphenhydramine as an adjunct sedative in high-risk patients (ie, patients on opioids). The primary aim of the present study was to determine whether the addition of diphenhydramine to conventional sedatives would reduce the dose of fentanyl and midazolam used during colonoscopy in individuals on chronic opioids. The secondary aims were to evaluate the effect of diphenhydramine use as an adjunct sedative on procedure-related times and to assess the tolerability and safety of adding diphenhydramine to conventional sedatives in patients on chronic opioids.

## METHODS

The present study was a single-center, prospective, randomized, double-blind, controlled trial conducted at the Oklahoma City Veterans' Affairs Medical Center (VAMC) between July 2014 and November 2016. The study was approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the Research and Development Office at the VAMC (number 3508). The study was registered at ClinicalTrials.gov (NCT T01967433).

### Population

Patients aged 18 to 75 years with a history of chronic opioid use undergoing screening, surveillance, diagnostic, or therapeutic colonoscopy with moderate sedation were included. We defined chronic opioid use as use of at least 5 mg of morphine or its equivalent at least 3 days per week for more than 3 months. Our exclusion criteria included inability to execute informed consent, allergy to diphenhydramine, fentanyl, or midazolam, pregnancy, history of colon resection, severe cardiopulmonary disease, and another endoscopic procedure scheduled on the same day.

### Design

Participants gave consent on the day of the procedure and were randomly assigned to receive either 10 mL (50 mg) of diphenhydramine or 10 mL of 0.9% sodium chloride (placebo). The randomization was performed by the research pharmacist at VAMC using the following website: http://www.randomization.com. The pharmacist also dispensed the study medication as a clear solution in identical unlabeled vials.

On the day of the procedure, participants were checked in and prepared according to the routine protocols of the endoscopy unit at the Oklahoma City VAMC. Each endoscopy team consisted of an attending gastroenterologist or an attending gastroenterologist with a gastroenterology fellow with at least 12 months of experience, and 2 nurses. Medications were administered by one of the nurses under the direct supervision of the physician. Research medication was administered 2 to 3 minutes before administration of other medications. At the start of the procedure, baseline vital signs were recorded per the unit's policy, and the study medication was administered intravenously. Neither the patient nor the medical staff, including the endoscopist, were aware of the contents of the vial. Moderate sedation (using the American Society of Anesthesiologists definition of maintaining purposeful response to verbal or tactile stimulation, adequate ventilation requiring no airway protection, and maintenance of cardiovascular function) was then achieved using incremental doses of the combination of intravenous midazolam (1 mg) and fentanyl (25 μg) given every 2 to 3 minutes. To minimize any crossover, additional diphenhydramine was not permitted.

During the procedure, vital signs, including oxygen saturation, were monitored at 3- to 5-minute intervals. Procedure-related adverse events, including hypoxia (defined as $O_2$ saturation less than 89% lasting for more than 30 seconds), hypertension (20 mm Hg increase in blood pressure from baseline, provided this is >140 mm Hg systolic and 90 mm Hg diastolic), hypotension (20 mmHg decrease in blood pressure from baseline, provided this is <100 mm Hg systolic or 60 mm Hg diastolic), bradycardia (a decrease in heart rate of >20 bpm, provided this is less than 60), tachycardia (an increase in heart rate of >20 bpm, provided this greater than 100 bpm), and use of reversal agents, ie, naloxone or flumazenil, were managed according to unit protocol and were recorded. After the procedure, the nurse and the fellow or the attending individually rated sedation qualitatively (inadequate, adequate, or oversedated) and quantitatively on a 7-point Likert scale (1, inadequate; 7 optimal sedation). Induction period (time from first dose of fentanyl to scope

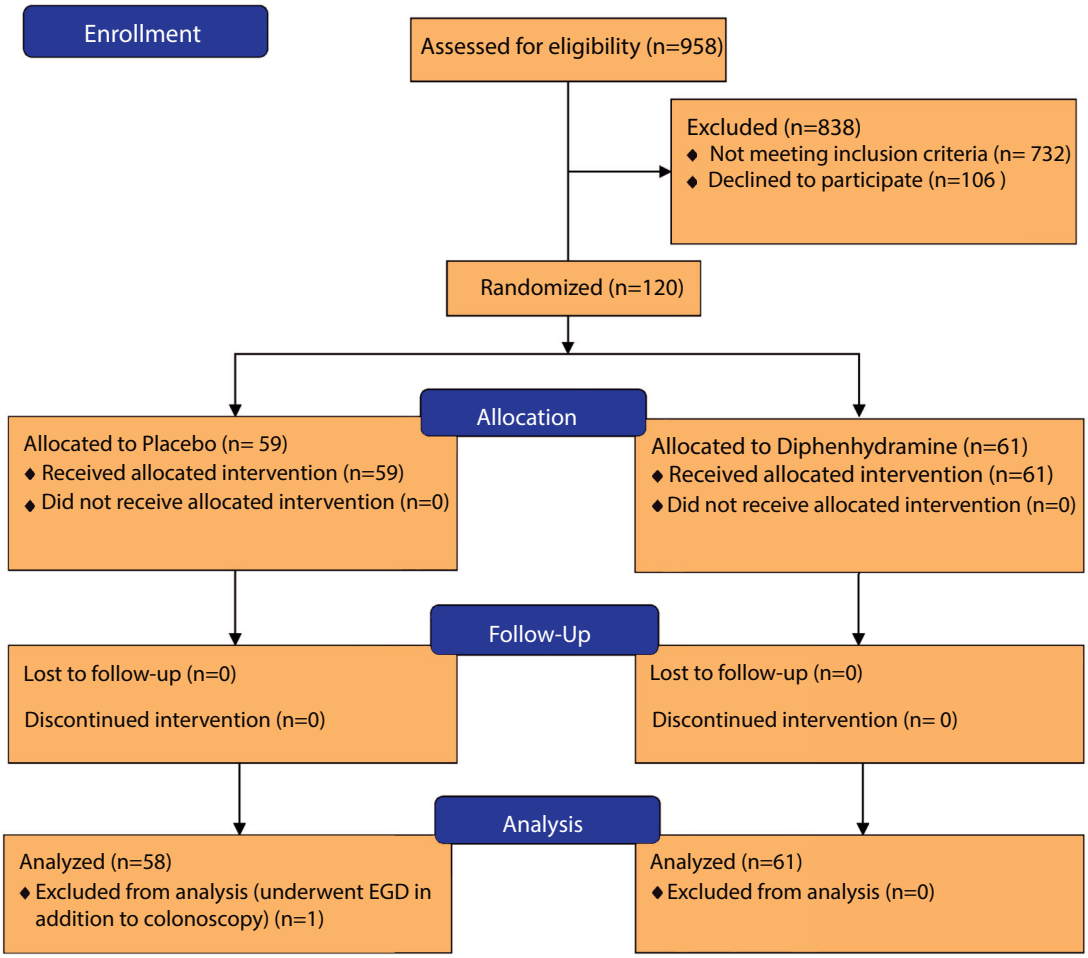


**Figure 1.** Flow diagram of patient enrollment.

insertion), procedural time (time from scope insertion to scope out), and recovery time (time from scope out to discharge) were recorded by the nursing staff in their standard documentation.

On the day after the procedure, patients received a follow-up phone call within 24 hours of discharge. Patients were asked to use a 10-point scale to evaluate the level of pain (1, no pain; 10, severe pain), and amnesia (1, complete memory; 10, no memory of procedure).

## Statistical analysis

**Sample size calculation.** Using data from our recently published study, we calculated a sample size of 120 to provide at least 80% power for detecting a 24.2 μg (or 20%) decrease in fentanyl dose between the diphenhydramine and placebo groups. In the sample size calculation, we assumed a standard deviation (SD) of 45.3 μg and a two-sided t test with a .05 significance level.[8] Descriptive analysis was presented for all factors. Continuous variables are reported as means ± SD and categorical variables are reported as percentages. Physicians', nurses', and patients' median (interquartile range [IQR]) assessment scores were also reported. The two-sided t test was used to compare the means of continuous variables (fentanyl dose, midazolam dose, induction time, procedure time, recovery time) in the 2 groups (diphenhydramine vs placebo). The chi-squared test was used to compare the categorical variables, including the proportions of side effects. Mann-Whitney test was used to compare medians between the 2 groups. A $P$ value $< .05$ was considered statistically significant. SAS software (SAS Institute, Cary, NC, USA) was used for data analyses.

## RESULTS

The first 120 patients who met the inclusion and exclusion criteria and provided informed consent were enrolled (Fig. 1). We randomly assigned 61 patients to the diphenhydramine group and 59 patients to the placebo

**TABLE 1. Patient characteristics**

| | Diphenhydramine (n = 61) | Placebo (n = 58) | *P* value |
|---|---|---|---|
| Age (years), mean ± SD | 60.7 ± 9.3 | 60.1 ± 9.7 | .71 |
| Male sex, n (%) | 57 (93.4) | 56 (96.6) | .43 |
| White race, n (%) | 45 (73.8) | 46 (77.6) | .34 |
| BMI (kg/m$^2$), mean ± SD | 30.4 ± 5.5 | 30.6 ± 6.8 | .83 |
| Indication | | | .6 |
| Screening, n (%) | 6 (9.8) | 7 (12) | |
| Surveillance, n (%) | 24 (39.3) | 21 (36.3) | |
| FIT positive, n (%) | 16 (26.3) | 17 (29.3) | |
| Abdominal pain, n (%) | 1 (1.6) | 1 (1.7) | |
| Hematochezia, n (%) | 9 (14.7) | 7 (12) | |
| Diagnostic other, n (%) | 5 (8.2) | 5 (8.6) | |
| Attending-only procedures, n (%) | 10 (16.4) | 9 (15.5) | .89 |
| Smoking, n (%) | 31 (50.8) | 24 (41.4) | .30 |
| Alcohol, n (%) | 20 (32.8) | 11 (18.9) | .17 |
| Drug abuse, n (%) | 11 (18) | 5 (8.6) | .26 |
| Anxiety, n (%) | 15 (24.6) | 17 (29.3) | .56 |
| Depression, n (%) | 38 (62.3) | 30 (51.7) | .24 |
| Morphine equivalent, mean ± SD | 37.9 ± 48.5 | 42.0 ± 40.1 | .62 |
| Duration of opioid use (months), mean (range) | 36 (12-72) | 42 (7-72) | .89 |
| Timing of last opioid dose | | | .80 |
| <12 hours | 10 (26.7) | 12 (24.4) | |
| >12 hours | 31 (73.3) | 33 (75.6) | |
| Type of opioid | | | .18 |
| Hydrocodone, n (%) | 45 (73.8) | 33 (56.9) | |
| Oxycodone, n (%) | 9 (14.8) | 8 (13.8) | |
| Hydromorphone, n (%) | 0 (0) | 0 (0) | |
| Morphine, n (%) | 3 (4.9) | 7 (12.1) | |
| Codeine, n (%) | 2 (3.3) | 1 (1.7) | |
| Methadone, n (%) | 1 (1.6) | 2 (3.5) | |
| Combination, n (%) | 1 (1.6) | 7 (12.1) | |
| Location of pain requiring treatment with opioids, n (%) | | | .54 |
| Abdominal, n (%) | 0 (0) | 0 (0) | |
| Musculoskeletal, n (%) | 60 (98.4) | 55 (94.8) | |
| Headache, n (%) | 0 (0) | 1 (1.7) | |
| Neuropathy, n (%) | 1 (1.6) | 1 (1.7) | |
| Malignant, n (%) | 0 (0) | 1 (1.7) | |
| Psychotropic medications | | | |
| TCA, n (%) | 8 (13.1) | 6 (10.3) | .64 |
| SSRI, n (%) | 29 (47.5) | 23 (39.7) | .69 |
| Antipsychotics, n (%) | 2 (3.3) | 5 (8.6) | .22 |
| Benzodiazepines, n (%) | 11 (18) | 15 (25.9) | .38 |
| Gabapentin, n (%) | 20 (32.8) | 30 (51.7) | .036 |

*SD*, Standard deviation; *BMI*, body mass index; *FIT*, fecal immunochemical test; *TCA*, tricyclic antidepressants; *SSRI*, selective serotonin receptor inhibitors.

**TABLE 2. Mean doses of sedatives used**

| Sedative | Diphenhydramine (n = 61) | Placebo (n = 58) | *P* value |
|---|---|---|---|
| Fentanyl (μg), mean ± SD | 125.4 ± 56.2 | 126.9 ± 53.5 | .88 |
| Midazolam (mg), mean ± SD | 4.9 ± 2.1 | 5.0 ± 1.9 | .79 |

*SD*, Standard deviation.

**TABLE 3. Quality of sedation**

| | Diphenhydramine (n = 61) | Placebo (n = 58) | *P* value |
|---|---|---|---|
| Mean physician score | 6.2 ± 1.1 | 5.3 ± 1.2 | .0002 |
| Mean nurse sedation score | 5.6 ± 1.5 | 5.1 ± 1.4 | .04 |
| Median physician score | 6 (6-7) | 5 (4-6) | <.0001 |
| Median nurse score | 6 (5-7) | 5 (4-6) | .02 |

**TABLE 4. Proportion of optimally sedated patients**

| | Diphenhydramine (n = 61) | Placebo (n = 58) | *P* value |
|---|---|---|---|
| Physician assessment, n (%) | 25 (71.4) | 10 (28.6) | .03 |
| Nurse assessment, n (%) | 29 (69.1) | 13 (30.9) | .001 |

group. One patient in the placebo group underwent an esophagogastroduodenoscopy along with colonoscopy, and therefore was not included in the analysis. The groups were comparable, and there were no statistically significant differences in baseline characteristics (Table 1). The mean age was 60.37 ± 9 years. Most participants were white males. Musculoskeletal pain was the most common reason for opioid use (Table 1). The daily opioid dose ranged between 5 and 385 morphine equivalents. The daily morphine equivalent dose and duration of opioid use were not statistically different between the groups (Table 1). The time of last opioid dose measured as either less than or greater than 12 hours before the procedure was available for 41 patients in the diphenhydramine group and 45 patients in the placebo group, and there was no significant difference between the groups (Table 1). Hydrocodone was the most commonly used opioid analgesic, and 82.5% of patients reported concomitant use of psychotropic medications (Table 1). Ten attending gastroenterologists, 9 gastroenterology fellows, and 12 nurses participated in study colonoscopies. Ten procedures in the diphenhydramine arm and 9 procedures in the placebo arm were performed by attending gastroenterologists alone ($P = .89$). Participating attending gastroenterologists and the gastroenterology fellows were uniformly distributed between groups ($P = .85$ and $P = .31$, respectively).

## Sedation dose

The mean dose of fentanyl required by the 2 groups was not statistically significantly different (125.4 ± 56.2 μg vs 126 ± 53.5, μg, $P = .88$). Similarly, the mean dose of midazolam was not statistically significantly different between the diphenhydramine and the placebo groups (4.9 ± 2.1 mg vs 5.0 ± 1.9 mg, $P = .79$) (Table 2).

## Quality of sedation

Most patients in both groups were adequately sedated. Qualitative analysis by physicians and nurses showed no significant difference between the groups. The physicians and nurses also independently measured the quality of sedation on a 7-point scale. The mean and median scores were significantly higher for the group receiving diphenhydramine: physician mean ± SD, 6.12 ± 1.1 versus 5.3 ± 1.2, $P = .0002$; physician median (IQR), 6 (6-7) versus 5 (4-6), $P < .0001$; nurse mean ± SD, 5.6 ± 1.5 versus 5.14 ± 1.4, $P = .04$; nurse median (IQR), 6 (5-7) versus 5 (4-6), $P = .02$ (Table 3). Patients in the diphenhydramine group were also more likely to receive a rating of optimal sedation by both physicians and nurses (Table 4). Mean patient-reported scores for pain and amnesia were significantly better in the diphenhydramine group: 2.05 ± 2.17 versus 3.09 ± 3.95, $P = .047$ and 7.8 ± 3.4 versus 6.5 ± 3.8, $P = 0.047$, respectively (Table 5). Median patient-reported scores for pain and amnesia showed a trend in favor of diphenhydramine use but did not reach statistical significance: 1 (1-1) versus 1 (1-5), $P = .06$ and 10 (9-10) versus 10 (7-10), $P = .06$, respectively.

## Time intervals

Procedure times were similar, with no statistically significant differences between the 2 study groups (Table 6). The mean induction time (6.4 ± 3.2 minutes vs 6.3 ± 2.8 minutes, $P = .86$), procedure time (34.8 ± 19.5 minutes vs 34.7 ± 17.8 minutes, $P = .98$), and recovery time (34.4 ± 9.2 minutes vs 32.4 ± 5.9 minutes, $P = .16$) were not significantly different between the 2 groups.

## Adverse events

The adverse event rate was low, and there were no major adverse events in either group (Table 7). Hypotensive episodes during the procedure were significantly more common in the placebo group (12 vs 22, $P = .027$). There was no significant difference in the number of hypertensive episodes between the 2 groups. There were no sedation-related hypoxic events, no patient required sedation reversal agents, and no additional adverse events were reported at the 24-hour follow-up.

**TABLE 5. Patient-reported scores**

| | Diphenhydramine (n = 61) | Placebo (n = 58) | *P* value |
|---|---|---|---|
| Patient pain score | 2.0 ± 2.17 | 3.09 ± 3.95 | .047 |
| Patient amnesia score | 7.8 ± 3.4 | 6.5 ± 3.8 | .047 |

**TABLE 6. Procedural times**

| | Diphenhydramine (n = 61) | Placebo (n = 58) | *P* value |
|---|---|---|---|
| Induction time (minutes), mean ± SD | 6.4 ± 3.2 | 6.3 ± 2.8 | .86 |
| Duration (minutes), mean ± SD | 34.8 ± 19.5 | 34.7 ± 17.8 | .98 |
| Recovery time (minutes), mean ± SD | 34.4 ± 9.2 | 32.4 ± 5.9 | .16 |

**TABLE 7. Procedural adverse events**

| | Diphenhydramine, n (%) | Placebo, n (%) | *P* value |
|---|---|---|---|
| Desaturation | 0 (0) | 0 (0) | |
| Tachypnea | 0 (0) | 0 (0) | |
| Apnea | 0 (0) | 0 (0) | |
| Hypotension | 12 (19.7) | 22 (37.9) | .027 |
| Hypertension | 5 (8.2) | 3 (5.2) | .51 |
| Arrhythmia | 0 (0) | 0 (0) | |
| Reversal agent use | 0 (0) | 0 (0) | |

## DISCUSSION

Over the last few decades, the use of opioids has increased among the general population. Further, it is often difficult to achieve and maintain adequate sedation in patients on chronic opioids.[11,12] Based on anecdotal data, the use of adjunct sedatives or deep sedation is often used with these patients.[19-23] Because of its hypnotic and sedative properties, diphenhydramine is recommended for endoscopic procedures in difficult-to-sedate patients, but the studies supporting its use have yielded conflicting results.[13,18] We designed a randomized controlled study to systemically analyze the use of diphenhydramine as an adjunct to routinely used sedatives in patients on chronic opioids. We did not observe a significant difference in the dose of fentanyl and midazolam, but our results did show improved sedation scores as assessed by the physician and the nurses in the diphenhydramine arm. In addition, use of diphenhydramine resulted in better patient-reported pain and amnesia scores without increasing the number of adverse events.

Similar to our study, a randomized trial conducted by Tu et al[18] evaluated the benefits of diphenhydramine use as an adjunct to meperidine and midazolam for screening colonoscopy. In their study, mean evaluation scores as judged by faculty, fellows, and nurses, were statistically significant in favor of the diphenhydramine group. Patient scores for overall sedation, pain level, and memory of the procedure were also statistically significantly lower in the diphenhydramine group compared with the placebo group.[18] There were no differences in induction, procedure, and recovery times.[18] In contrast to our results, Tu et al did observe a significant reduction in the amount of traditional sedatives used during colonoscopy in the diphenhydramine arm. The lack of difference in the amount of fentanyl and midazolam observed between the 2 groups in our study may have several explanations beyond the effectiveness of diphenhydramine. It is possible that the initial doses in the placebo arm were closely staggered, resulting in hemodynamic changes (eg, hypotension) that prevented the physician from administering additional doses of traditional sedatives. In addition to more side effects in the placebo arm, it is possible that providers were not comfortable using a dose above a certain numerical value, which could have contributed to a lack of difference in mean medication doses between the groups. It is unlikely that the timing of diphenhydramine administration contributed to a difference in the observed results as we used a dosing schedule similar to that in the Tu et al study.

In a more recent study by Sachar et al,[13] continued use of midazolam was found to be superior to diphenhydramine in difficult-to-sedate patients. In this study, patients who were unable to achieve adequate sedation after 100 μg of fentanyl and 5 mg of midazolam were randomized to receive either diphenhydramine or midazolam.[13] If adequate sedation was not achieved after 3 doses of study medication (total of diphenhydramine 75 mg or midazolam 4.5 mg), the patient was considered to have failed to achieve the primary endpoint.[13] The primary endpoint was achieved less often with diphenhydramine than with midazolam. Patients in the diphenhydramine group also required higher doses of fentanyl and midazolam to achieve similar post-procedure physician and patient assessment scores.[13] Subgroup analysis including patients on opioids favored continued midazolam use.[13] There were, however, some key differences between the present study and the study conducted by Sachar et al.[13] First, in the present study, diphenhydramine was used an adjunct to a combination of fentanyl and midazolam, whereas in the Sachar et al study, diphenhydramine was used as a substitute for midazolam. Second, we chose to give diphenhydramine before the first dose of fentanyl and midazolam. Our dosing schedule, although different from American Society for

Gastrointestinal Endoscopy guidelines, was based on pharmacokinetic properties and is supported by the results of Tu et al.[18] The timing of the diphenhydramine dose may have contributed to our favorable results; therefore, our results could be used as an argument to administer diphenhydramine at the start of the procedure based on the pre-procedure assessment.

Adverse events were rare, and our study was not powered to detect differences in individual adverse events. However, we observed a higher incidence of hypotension episodes in the placebo arm. In addition to the mechanism suggested above, it is possible that the anti-histaminic effects of diphenhydramine protected against hypotension. Studies have shown that some opiates can trigger a histamine response, and it is plausible the diphenhydramine mitigated this effect in some patients.[24]

Inability to achieve adequate sedation is often quoted as a reason to use deep sedation in patients on chronic opioids.[15] However, our results indicate that colonoscopies can be safely completed in this patient population using moderate sedation with diphenhydramine as an adjunct. All procedures in the present study were successfully completed, with a cecal intubation rate of 100%. There were no major procedure-related adverse events and few side effects. Most patients reported good control of pain and amnesia. In the active arm, the physician graded sedation as adequate for all but 1 patient. Our results thus argue against the mandatory use of deep sedation to achieve adequate sedation in this group of patients. Our argument is further supported by earlier studies that have shown that although propofol has a more rapid onset of action and shorter recovery time than do traditional sedatives, it does not improve other clinically important outcomes.[25-27]

Although the present study is unique in that it explores the utility of adjunct sedatives in a difficult-to-sedate patient population, it is not without limitations. We recruited only veterans; therefore, the main limitation is that most of our patients were white males. More than 90% of our patients were older than 55 years of age. Therefore, our results might not be generalizable to other populations. We also restricted enrollment to patients who were on chronic opioids and were undergoing outpatient colonoscopies. Our results therefore should not be generalized to either different patient cohorts or other procedures. A history of substance abuse, depression, anxiety, and use of psychotropic medications were common and likely representative of our unique patient cohort. In our study, significantly more patients in the traditional sedation group were on gabapentin, which can potentially have an impact on sedation requirements. However, our post hoc subgroup analysis comparing patients on gabapentin with those who were not on gabapentin found no significant differences in fentanyl dose ($P = .1$), midazolam dose ($P = .36$), physician assessment score ($P = .66$), nurse rating ($P = .30$), patient pain score ($P = .80$), and amnesia score ($P = .56$). One potential limitation is the possibility that blinding of physicians and nurses may have been compromised during the 2 to 3 minutes after the diphenhydramine administration before the first dose of fentanyl and midazolam. However, we did not observe any significant sedative effect during this period and, given the volume of distribution of 4.5 L/kg for intravenous diphenhydramine, it is highly unlikely any significant central nervous effect would be detectable within 2 to 3 minutes, particularly in this difficult-to-sedate population.[28] Finally, our small sample size and low rate of adverse events makes it difficult to meaningfully compare the rates of individual adverse events.

From the present study, we conclude that in patients on chronic opioid therapy, administration of diphenhydramine at the start of colonoscopy, in combination with other conventional sedatives, does not allow for lower doses of conventional sedatives but improves the quality of sedation. Our results suggest that the use of diphenhydramine would improve the experience of this group of patients who have traditionally been difficult to sedate. Further studies to identify the characteristics of patients with inadequate sedation and doses outside the recommended range, despite use of diphenhydramine as an adjunct, will help to better streamline the care of these patients.

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