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ORIGINAL RESEARCH

# Effects of Loratadine/Montelukast on Vigilance and Alertness Task Performance in a Simulated Cabin Environment

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## ABSTRACT

***Introduction:*** Sedating effects of some medications used to treat allergic rhinitis (AR) symptoms can impair an individual's ability to function optimally. The objective of this study was to characterize the effects of a single dose of loratadine/montelukast (L/M) versus placebo and diphenhydramine on daytime somnolence and psychomotor performance in healthy volunteers. ***Methods:*** In this single-center, randomized, double-blind, placebo- and active-controlled, three-way crossover study, healthy volunteers received single doses of placebo, L/M 10 mg/10 mg, and diphenhydramine 50 mg. Subjects ($n$=23) were evaluated under simulated cabin pressure using the following tools: Vigilance and Tracking Task (VigTrack), measuring vigilance and tracking performance; the Multi-Attribute Task Battery (MAT), measuring ability to perform multiple tasks simultaneously; and the Stanford Sleepiness Scale (SSS), measuring sedative effects of medication, at baseline and each hour from 1 to 6 hours postdose. Safety was monitored via adverse events and vital signs. ***Results:*** Performances on VigTrack and MAT from 1 to 6 hours after dosing were not significantly different between L/M and placebo groups; in contrast, diphenhydramine resulted in significant impairment of tracking for up to 5 hours ($P$≤0.01) and vigilance performance for up to 3 hours ($P$≤0.05) on VigTrack versus placebo. Scores of subjective sleepiness as measured by SSS were similar for patients treated with L/M versus placebo, whereas significant increases in sleepiness occurred between 1-5 hours posttreatment in diphenhydramine-treated patients versus placebo-treated patients ($P$≤0.05). ***Conclusions:*** L/M is similar to placebo in effects on daytime somnolence and psychomotor performance. L/M treatment resulted in significantly less sleepiness and impairment of vigilance and tracking than diphenhydramine.

**Keywords:** antihistamine; antileukotriene; cognitive performance; diphenhydramine; loratadine/montelukast; Multi-Attribute Task Battery; quality of life; seasonal allergic rhinitis; Stanford Sleepiness Scale; Vigilance and Tracking Task

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## INTRODUCTION

Recognized as a common global health issue, allergic rhinitis (AR) affects at least 10% to 25% of the world's population, based on current estimates.[1] The symptoms of AR include nasal congestion, rhinorrhea, nasal itching, sneezing, and itchy/watery eyes, and can have a considerable impact on an individual's ability to perform daily tasks.[2] Fatigue, headaches, malaise, and "feeling miserable" are common complaints of individuals with AR.[1,3,4] AR symptoms also negatively influence quality of life (QOL) and may lead to impairment of school performance or work productivity.[2,5-7] A large US survey ($n$=2355) concerning AR symptoms rated nasal congestion as the most bothersome AR symptom and the symptom they most wished to prevent.[5] Nasal congestion itself has been linked to sleep disruptions, emotional disturbances, and decreased work productivity.[4,5,8]

Not only do symptoms of AR adversely affect patients' ability to function in daily life, so do the side effects associated with some pharmacotherapies used for AR treatment. Many first-generation antihistamines, such as diphenhydramine, have been shown to produce sedation and reduced QOL.[9] Second-generation antihistamines also may produce varying levels of drowsiness or impairment, especially when used at higher than recommended doses.[10] Impairment, defined as the decrease or absence of a physical or mental ability, can be assessed objectively, whereas drowsiness, defined as state of sleepiness or lethargy, is a subjective measure.[10] Sedation encompasses both symptoms of drowsiness and measures of impairment.[10] In this context, QOL encompasses not only the occurrence of physical symptoms but also the ability of individuals to perform tasks.[9]

The impact of these effects on individuals' ability to function has been studied in aircraft pilots, for whom impairment resulting from medications would be a major concern.[11] Pilots must remain attentive, maintain vigilance under monotonous conditions, and be able to perform complex psychomotor tasks, including rapid decision-making.[12,13] These functions are particularly vulnerable to the sedative effects of medications,[11,14,15] which may be further amplified by the low-pressure environment of the cockpit.[16,17] Therefore, simulated cockpit conditions may represent more rigorous conditions under which the sedative effects of medications can be studied.

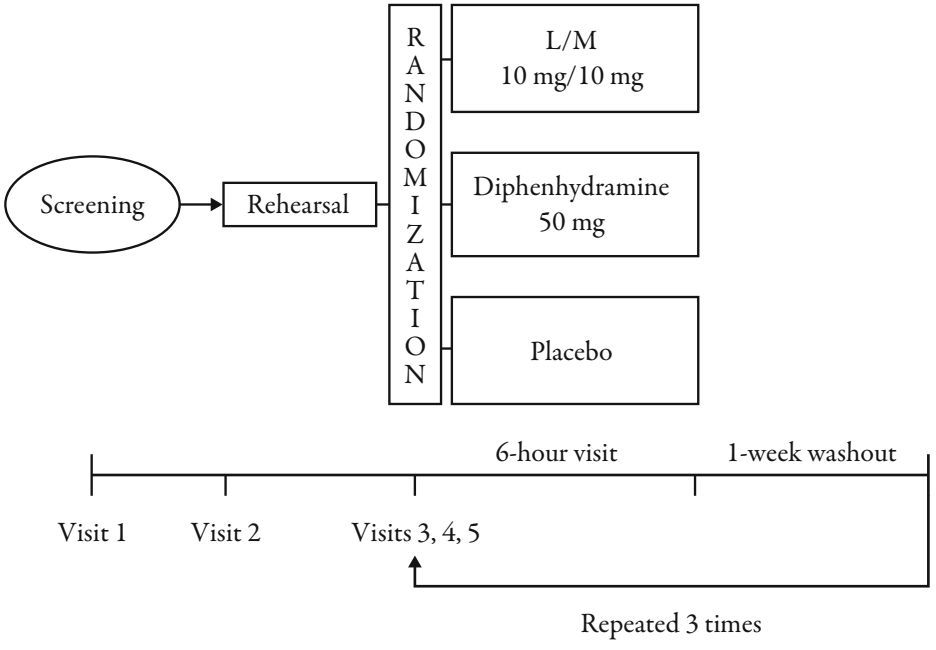
We sought to rigorously characterize the effects of a single dose of loratadine/montelukast (L/M), relative to placebo, on psychomotor performance and daytime somnolence in healthy volunteers under simulated cabin pressure (hypobaric) conditions measured by tools established to determine antihistamine-associated sedation effects: the Vigilance and Tracking Task (VigTrack), the Multi-Attribute Task Battery (MAT), and the Stanford Sleepiness Scale (SSS).[18] Diphenhydramine 50 mg, an antihistamine with well-documented sedative side effects and detrimental effects on cognitive and psychomotor performance,[19] was included in the study as an active control.

## MATERIALS AND METHODS

### Study Design

In this phase 2, single-center, randomized, double-blind, placebo- and active-controlled, three-way crossover study conducted in The Netherlands, subjects received a single dose of L/M 10 mg/10 mg, diphenhydramine 50 mg, or placebo on a three-way crossover basis, such

**Figure 1.** Study design.




that each subject had received one dose of all three treatments by completion of the study (Figure 1). Each study drug was administered in the morning, with at least a 7-day washout period between treatment visits. At each of the three treatment visits, under staff supervision, subjects entered a hypobaric chamber, and the ambient pressure was decreased to 75.2 kPa (equating to a cabin altitude of 8000 feet). Subjects completed all performance tasks and the SSS, and had peripheral hemoglobin-oxygen saturation ($SaO_2$) measured prior to baseline and 1, 2, 3, 5, and 6 hours after receiving study medication. Pressure in the hypobaric chamber was increased to a level equivalent to that at sea level 6.5 hours after dosing; at hour 7, subjects underwent a medical evaluation and were subsequently allowed to return home. So that they would be familiar with testing procedures, study participants received training on the performance tests at a "rehearsal" visit occurring after the initial screening and within 7 days of the first treatment visit. "Ear sinus checks" were also performed at this visit to determine subjects' tolerance of pressure changes in the hypobaric chamber. Those experiencing severe pain were excluded from the trial.

On each treatment day, subjects were instructed to eat a light, standardized breakfast at home; during the treatment visit they were given a standardized lunch and allowed to drink mineral water, decaffeinated coffee, and fruit juices. On the day preceding a treatment visit, study participants were limited to three 8-ounce cups of coffee or tea. Alcohol was not permitted on the day before and the day of treatment. Physical exercise also was prohibited on treatment days, and activities were provided for subjects to avoid daytime somnolence from boredom or lack of interest. Subjects' quality of sleep on the night before a treatment visit was assessed using the Groningen Sleep Quality Scale (GSQS) (0 = minimum score; 14 = maximum score; a score

of ≥6 on the GSQS indicates a poor night of sleep), a tool that has been used to measure sleep disturbances in multiple Dutch studies of airline pilots.[20]

The investigator, patients, and study center staff were blinded to treatment assignment. To maintain blinding, at each treatment visit subjects received one capsule and one tablet according to the following pattern: active treatment tablet (L/M) + placebo capsule, active treatment capsule (diphenhydramine) + placebo tablet, or placebo capsule + placebo tablet. Active treatment capsules and tablets were identical in appearance and packaging to placebo capsules and tablets. Before trial initiation, the study protocol and informed consent statement were reviewed and approved by the Independent Ethics Committee of the Central Military Hospital (Center P02192-001) of The Netherlands. The trial was performed according to Good Clinical Practice and International Conference on Harmonisation standards and guidelines, and participants gave written informed consent prior to undergoing any trial-related procedures.

**Subjects**

Subjects were recruited via advertisement in local newspapers. The study population comprised healthy, nonsmoking male volunteers aged 18 to 40 years. A decision was made to include only male subjects because of complicating factors such as monthly periods, hormones, and pregnancy testing.

General good health was confirmed by routine clinical and laboratory testing, with complete blood count, blood chemistries (including total protein, creatinine, albumin, sodium, calcium, potassium, total bilirubin, chloride, alkaline phosphatase, alanine aminotransferase, glucose, aspartate aminotransferase, phosphorus, blood urea nitrogen, cholesterol, and lactate dehydrogenase), and urinalysis results all within normal limits or deemed acceptable by the investigator. Participants also were required to weigh within 10% of normal body weight for their height and frame size. Subjects who had a positive urine test result for drugs with high abuse potential or any clinically significant disease that would interfere with participation in the study were excluded. Other exclusion criteria were active seasonal and/or perennial AR, an upper respiratory tract or sinus infection, a viral upper respiratory infection within 7 days of screening, a history of or current chronic illness, a history of psychotic disorder(s), drug addiction or abuse of drugs or alcohol, and the need to take medication for central nervous system disorders or to take any medication having sedative effects. Other prohibited medications included corticosteroids (except topical), antihistamines, leukotriene antagonists/inhibitors, decongestants, and anticholinergic agents. To participate in the study, subjects who used prohibited medications were required to have discontinued them for 3 months to 7 days prior to the rehearsal visit, with the exact washout period depending on the specific medication type. In total, 27 healthy male volunteers were recruited. Four of them did not enter the trial: one volunteer had the flu at the first trial day; the other three did not meet protocol eligibility. The remaining 23 subjects met all criteria of the study protocol.

**Psychomotor Performance and Safety Assessments**

All measures were assessed at baseline and

1, 2, 3, 5, and 6 hours after administration of study drug. The effect of study medication on participant psychomotor performance was assessed using the VigTrack and the MAT. The VigTrack[18] performance measures assessed in the study included root mean square (RMS) of the tracking error, the percentage of omissions, and the number of false reactions. Sensitivity of the VigTrack for measuring antihistamine-associated sedation effects has been established previously.[18] The MAT is also computer-based and is comprised of a system-monitoring task, a tracking task, a communication task, and a fuel management task, all of which the participant completes simultaneously on a display screen during a 10-minute period. Tasks mimic those an airplane pilot would perform during flight, such as monitoring fuel levels and communicating with air traffic control. Performance assessments for the MAT test analyzed in the trial included the number of false reactions, omissions, and adequate responses; mean response, decision, and reaction times; RMS of the tracking error; and mean absolute deviation from fuel target. In addition, participants completed the SSS (1 = alert, wide awake; 7 = sleep being imminent, losing struggle to remain awake) as a subjective measure of the sedative effects of study medications. Oxygen saturation ($SaO_2$) was also measured.

Safety evaluations included the incidence of adverse events (AEs) and changes in vital signs.

### Statistical Analyses

Eligible subjects were randomized according to a computer-generated schedule using all six treatment sequences to ensure balance for first-order carry-over effect in this three-way crossover designed study.

It was determined that a sample size of 24 subjects completing all three treatment visits would ensure an 80% power to detect a difference of 0.82 standardized units (two-tailed 0.05 significance level). Having 23 will affect the power calculation in such a way that power is decreased to 77%: a percentage that is assumed to be still adequate for this study.

Analysis of variance (ANOVA) was used to test for significant carry-over effects for VigTrack and MAT variables, and none were detected. Treatment differences at each time point were then analyzed using a second ANOVA model. If a significant overall difference was found ($P<0.05$), $F$ tests were used to analyze the different contrasts. In addition, confirmatory analyses were performed for VigTrack, MAT, and SSS results using Student's paired $t$ tests and Wilcoxon matched-pairs signed rank tests, with the placebo group included for reference. Results of all statistical analyses were considered significant at a $P<0.05$ significance level.

## RESULTS

### Subject Disposition

Twenty-three subjects were randomized into the study. All randomized subjects completed the trial, with no protocol deviations or study withdrawals, and comprised the intent-to-treat (ITT) analysis population. Subjects' ages ranged from 19 to 31 years (mean, 23 years 7 months). Mean weight was 74.6 kg (range, 59-109 kg), and mean height was 182.7 cm (range, 170-195 cm). Data from the three treatment periods were similar with respect to baseline subjective sleep quality prior to each visit as measured using the GSQS.

**Figure 2.** Change over time from baseline in VigTrack: tracking ability (root mean square error) of subjects over 6 hours. Relative to baseline, positive scores reflect impaired performance and negative scores reflect improved performance. *$P$<0.01 versus placebo. †$P$<0.001 versus placebo.

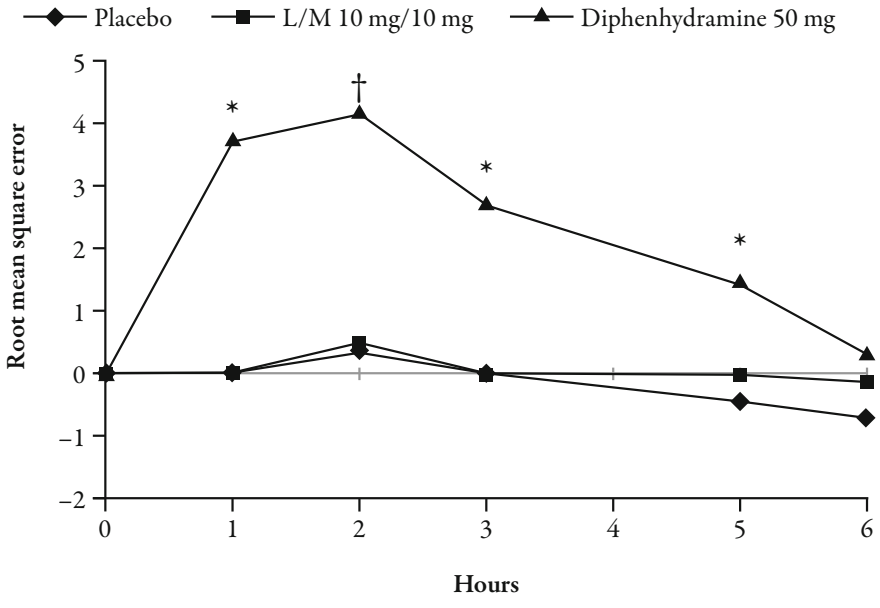
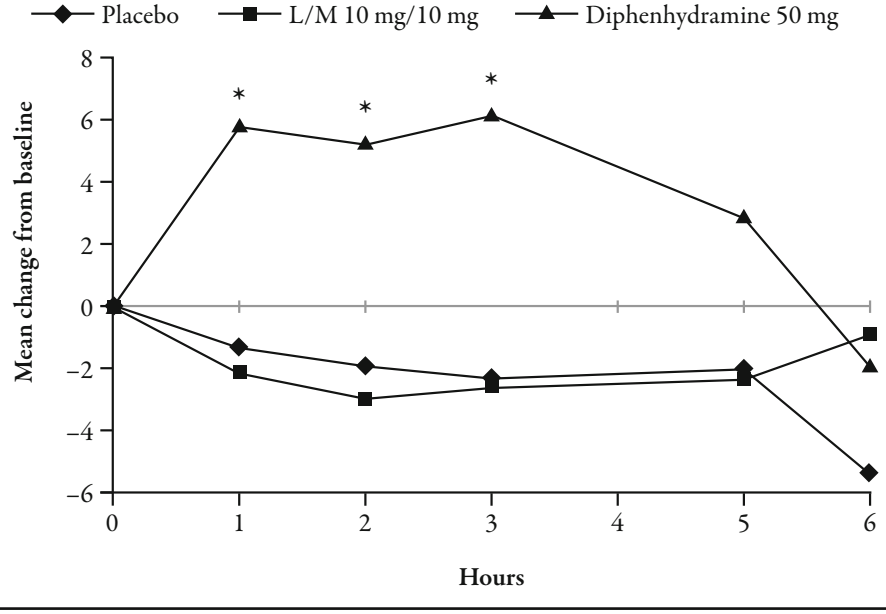



**Figure 3.** Change over time from baseline in VigTrack: vigilance (% omissions of response) of subjects over 6 hours. Relative to baseline, positive scores reflect impaired performance and negative scores reflect improved performance. *$P$<0.05 versus placebo.



## Psychomotor Performance and Sedation Effects

### *Vigilance and Tracking Task (VigTrack)*

Mean baseline VigTrack scores were comparable among all treatment groups. No significant differences in tracking (Figure 2) or vigilance scores (Figure 3) between L/M and placebo were present at any time point after dosing. In contrast, significant impairment was observed with diphenhydramine compared with L/M and placebo ($P<0.05$ and $P<0.01$, respectively) for the tracking parameter of RMS error for each time point up to 5 hours postreatment. Similarly, diphenhydramine significantly impaired performance versus L/M and placebo ($P<0.05$ for both) based on the vigilance parameter of percentage of omissions for each time point up to 3 hours posttreatment. Differences between treatments for the vigilance parameter of number of false reactions were not statistically significant.

### *Multi-Attribute Task Battery (MAT)*

There were no significant differences between L/M and placebo for any parameter of task performance as measured by the MAT. In contrast, administration of diphenhydramine resulted in significant impairment versus placebo and L/M for several tasks. Tracking performance (RMS error) was significantly impaired by diphenhydramine compared with placebo for the first 2 hours after treatment, and performance for the communication parameter of number of adequate responses was significantly reduced by diphenhydramine during the first 2 hours posttreatment compared with L/M ($P<0.05$ for both). Diphenhydramine also resulted in dis-

**Figure 4.** Change over time from baseline in sleepiness of subjects over 6 hours. The Stanford Sleepiness Scale was used to measure subject-reported sleepiness on a scale of 1 (alert) to 7 (sleep being imminent). *$P<0.05$ versus placebo.

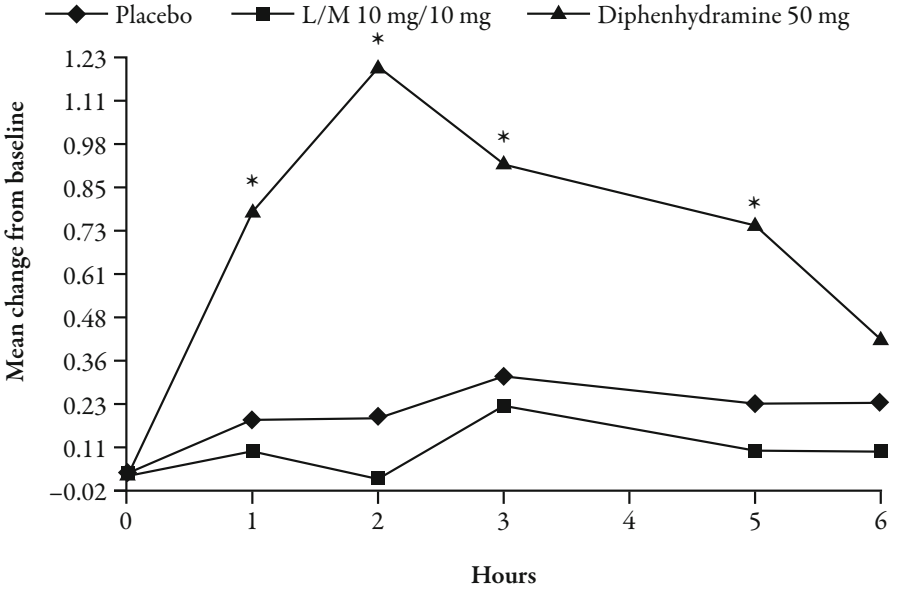


**Table 1.** Incidence of all treatment-emergent adverse events.

| | Number (%) of subjects | | |
|---|---|---|---|
| | L/M 10 mg/10 mg (*n*=23) | Diphenhydramine 50 mg (*n*=23) | Placebo (*n*=23) |
| **Subjects reporting any adverse event** | **1 (4)** | **3 (13)** | **3 (13)** |
| **Body as a whole—general disorders** | **0** | **1 (4)** | **0** |
| Fatigue | 0 | 1 (4) | 0 |
| Headache | 0 | 1 (4) | 0 |
| **Gastrointestinal system disorders** | **1 (4)** | **0** | **1 (4)** |
| Abdominal pain | 1 (4) | 0 | 0 |
| Diarrhea | 0 | 0 | 1 (4) |
| **Hearing and vestibular disorders** | **0** | **0** | **1 (4)** |
| Sensation of block in ear | 0 | 0 | 1 (4) |
| **Respiratory system disorders** | **0** | **2 (9)** | **1 (4)** |
| Sinus congestion | 0 | 1 (4) | 0 |
| Upper respiratory tract infection | 0 | 1 (4) | 1 (4) |

turbances in fuel management task performance immediately after dosing that returned to baseline level after 3 hours, as well as in longer reaction times for system-monitoring tasks. However, these differences from the other treatment groups did not reach statistical significance.

### *Stanford Sleepiness Scale (SSS)*

Scores on the SSS test indicating subjective daytime sleepiness were comparable between L/M and placebo groups for the entire posttreatment period (Figure 4). However, somnolence was significantly increased in diphenhydramine-treated subjects for up to 5 hours after dosing compared with subjects receiving placebo ($P<0.05$).

### Safety

Three subjects each in the placebo- and diphenhydramine-treated groups reported a combined total of seven AEs during treatment, and one subject receiving L/M treatment reported an AE (abdominal pain) (Table 1). One subject experienced AEs during both placebo (diarrhea) and diphenhydramine treatment (upper respiratory tract infection). All AEs were considered mild in severity, none led to withdrawal from the study, and only two (fatigue and headache occurring during diphenhydramine treatment) were considered related to study drug. No serious AEs were reported during the study. No significant abnormalities in vital signs were observed.

## DISCUSSION

In this study, L/M administered in a single dose did not result in detrimental effects compared with placebo on the performance of standardized activities designed to measure mental acuity and alertness, including vigilance, tracking, and complex tasks, for up

to 6 hours after dosing. Moreover, L/M- and placebo-treated patients had similar scores for subjective sleepiness on the SSS, indicating a lack of sedative effect for L/M. These results are not surprising, given that loratadine has not been associated with sedative effects or impairments on psychomotor performance.[10,18,19,21] Diphenhydramine significantly increased subjective sleepiness and impaired the performance of mental acuity tasks in the current study, as has been shown in previous investigations.[10,19]

In daily practice antihistamines will often be prescribed for an extended period. Possible sedative effects of multiple dosing and/or prolonged therapy were not addressed in this study.

Several studies have examined the sedative effects of AR therapies using comprehensive measures of psychomotor performance and/or sedation. For example, the CogScreen battery showed that measures of perceptual speed, divided attention, working memory, and vigilance were impaired with diphenhydramine.[19] Furthermore, in one crossover study using the Iowa Driving Simulator ($n$=40), individuals taking diphenhydramine 50 mg performed in driving tests as poorly as or more poorly than those with blood alcohol levels at about the legal limit (0.1%) in most US states.[22] These impairments of attention, vigilance, memory, and psychomotor performance have been observed with diphenhydramine even in patients who do not report feeling sleepy.[19] Despite these well-documented effects, diphenhydramine is the most widely used antihistamine in the US[10] and is readily available over the counter.

In conclusion, L/M lacks the sedative effects typical of diphenhydramine that may have an impact on patient QOL, including the ability to function at work and school.

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