Efficacy and Safety of Doxepin 1 mg, 3 mg, and 6 mg in Adults with Primary Insomnia

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Study Objectives: To evaluate the efficacy and safety of doxepin 1, 3, and 6 mg in insomnia patients.

Design: Adults (18-64 y) with chronic primary insomnia (DSM-IV) were randomly assigned to one of four sequences of 1 mg, 3 mg, and 6 mg of doxepin, and placebo in a crossover study. Treatment periods consisted of 2 polysomnographic assessment nights with a 5-day or 12-day drug-free interval between periods. Efficacy was assessed using polysomnography (PSG) and patient-reported measures. Safety analyses included measures of residual sedation and adverse events.

Measurements and Results: Sixty-seven patients were randomized. Wake time during sleep, the a priori defined primary endpoint, was statistically significantly improved at the doxepin 3 mg and 6 mg doses versus placebo. All three doses had statistically significant improvements versus placebo for PSG-defined wake after sleep onset, total sleep time, and overall sleep efficiency (SE). SE in the final third-of-the-night also demonstrated statistically significant improvement at all doses. The doxepin 6 mg dose significantly reduced subjective latency to sleep onset. All three doxepin doses had a safety profile comparable to placebo. There were no statistically significant differences in next-day residual sedation, and sleep architecture was generally clinically preserved.

Conclusions: In adults with primary insomnia, doxepin 1 mg, 3 mg, and 6 mg was well-tolerated and produced improvement in objective and subjective sleep maintenance and duration endpoints that persisted into the final hour of the night. The side-effect profile was comparable to placebo, with no reported anticholinergic effects, no memory impairment, and no significant hangover/next-day residual effects. These data demonstrate that doxepin 1 mg, 3 mg, and 6 mg is efficacious in improving the sleep of patients with chronic primary insomnia.

Keywords: Chronic insomnia, sleep maintenance insomnia, terminal insomnia, doxepin, wake time after sleep onset, total sleep time, wake time during sleep

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INTRODUCTION

CHRONIC INSOMNIA IS THE MOST PREVALENT SLEEP DISORDER, AFFECTING AN ESTIMATED 10%-16% OF THE ADULT POPULATION, WITH AN ADDITIONAL 25% TO 35% HAVING TRANSIENT OR OCCASIONAL INSOMNIA. Primary insomnia is estimated to have a prevalence of 1% to 2% in the general population, but accounts for as much as 25% of all chronic insomnia cases seen in clinical contexts. Insomnia generally does not resolve spontaneously and tends to be chronic in nature, with 83% of patients with chronic disorders and insomnia reporting continuing problems with insomnia at a 2-year follow-up period.

Pharmacotherapy is the predominant treatment among medical practitioners for insomnia management primarily because of availability. The most commonly used pharmacologic agents approved for the treatment of insomnia include zolpidem, temazepam, and eszopiclone. These agents all have a similar mechanism of action, acting on the benzodiazepine receptor of the gamma-aminobutyric acid (GABA) complex. This class of agents has been associated with side-effects such as daytime sedation, motor incoordination, cognitive impairment, and related concerns about increases in the risk of motor vehicle accidents and injuries from falls. These agents have also been associated with the potential for abuse and dependence in at-risk populations, which led the
U.S. Drug Enforcement Agency to classify them as Schedule IV substances.

Despite the lack of Food and Drug Administration (FDA) approval for the treatment of insomnia and the relative lack of efficacy and safety data at hypnotic doses, sedating antidepressants such as trazodone are commonly used in clinical practice. However, the limited available data on the use of these agents indicate that when used for insomnia at antidepressant doses they are associated with undesirable side-effects. Additionally, the efficacy, safety, and optimal dosages of these drugs have not been systematically defined.10

Doxepin, a compound with potent histamine blocking activity (mainly H1), has long been known to have significant sleep promoting effects.11 Three randomized, placebo-controlled trials have examined this sleep effect in primary insomnia patients. The first 2 studies assessed sleep patterns in 10 patients after both intravenous (single injection) and oral administration (3 weeks) of doxepin 25 mg or placebo in a crossover design,12,13 with the third examining the effect of doxepin 25 to 50 mg administered orally in a 4-week trial.14 Efficacy results for all 3 studies indicated that nightly doxepin administration significantly improved polysomnographic (PSG) sleep measures versus placebo, including total sleep time (TST) and wake time after sleep onset (WASO).12-14

Although doxepin has demonstrated efficacy in promoting sleep in insomnia patients, the optimal hypnotic dosages and safety at these doses have not been systematically defined. Similar to the other commonly prescribed compounds used off-label to treat insomnia, doxepin at doses ≥25 mg is associated with undesirable side effects, including significant anticholinergic effects.11,14 Additionally, when used at these higher doses, the selectivity of doxepin for H1 receptors is compromised because the other less selective receptor systems take on additional physiological importance.15,16

The current study assessed doxepin at doses of 1 mg, 3 mg, and 6 mg; doses many-fold lower than previously studied in insomnia patients, to determine whether the efficacy would be retained in the presence of a good safety and tolerability profile. Positive results at these low doses would suggest the pharmacologic profile of an H1 selective antagonist.

METHODS

The present study was a randomized, multi-center, double-blind, placebo-controlled, four-period crossover, dose-response study designed to assess the efficacy and safety of 3 doses of doxepin (1 mg, 3 mg, and 6 mg) compared with placebo in patients with chronic primary insomnia.

Patients

Eligible patients were men and non-pregnant, non-lactating women 18 to 64 years of age, inclusive. Two hundred and thirty patients were screened for study participation. This initial screening was used to verify that all patients had the following: (1) a DSM-IV diagnosis of primary insomnia for at least the last 3 months; (2) a reported total sleep time (sTST) ≤6.5 hours; (3) a reported wake time after sleep onset (sWASO) ≥60 min; and (4) a reported latency to persistent sleep (LSO) ≥20 min, all on ≥4 nights per week prior to PSG screening. Patients were excluded from the study if they reported: (1) Consuming >4 alcoholic beverages in a day, or >15 alcoholic beverages weekly within the 14 days before screening; (2) using nicotine-containing products moderately (≥15 cigarettes daily), or using nicotine-containing products within 30 min of bedtime, during the middle of the night, or within 30 min of awakening; (3) consuming >5 caffeine-containing beverages a day, or self-reported consumption of any caffeine-containing product within 6 hours of study drug dosing; (4) intentionally napping >2 times/week; (5) having a variation in bedtime ≥2 hours on 5 of 7 nights, based on screening sleep diaries; (5) having a history of cognitive disorders, depression, schizophrenia, panic disorder, dementia, chronic pain, glaucoma, or frequent nightly urination (>2 times per night); (6) having tested positive at screening for screening for hepatitis B surface antigen or hepatitis C antibody, or having a positive urine drug screen for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, or cannabinoids; (7) using a hypnotic or any other medication known to affect sleep; or (8) using any medication known to affect the central nervous system, including anxiolytics, antidepressants, anticonvulsants, narcotic analgesics, antipsychotics, appetite suppressants, systemic corticosteroids, respiratory stimulants, and decongestants. All patients gave written informed consent prior to screening assessments.

Those patients meeting screening criteria (n = 184) completed PSG evaluation to determine whether they met PSG screening criteria. Two consecutive nights of PSG screening were conducted; patients were required to have a latency to persistent sleep (LPS) ≥10 min, a wake time during sleep (WTDS) ≥60 min with no night <45 min and a total sleep time (TST) ≥240 and ≤410 min in order to be eligible for randomization. Patients were excluded from the study during PSG screening if they had periodic limb movement disorder (≥10 periodic limb movements with arousal per hour of sleep) or sleep apnea (≥10 apnea/hypopnea events per hour of sleep).

Sixty-seven patients met all entry criteria and were randomly assigned to one of four treatment sequences in a 1:1:1:1 ratio using a Latin square design. Enrollment from the 11 investigational sites ranged from 2 to 11, with a mean of 6.1 patients per site. The Institutional Review Board for each study site approved the protocol, and the study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practices. Patients were compensated for their participation.

Procedure

Eligible patients were randomized to a treatment sequence such that all patients received all treatments (doxepin 1 mg, 3 mg, and 6 mg, and placebo). Each patient completed five 2-day assessment periods (including single-blind placebo screening period and 4 treatment periods) with a 5- or 12-day drug-free interval between Treatment Periods. During each Treatment Period, patients received 2 consecutive nights of study drug dosing, followed by 8 hours of PSG recording in a sleep laboratory. Efficacy assessments were made at each visit, and safety assessments were performed throughout the study. Patients were allowed to leave the sleep laboratory during the day. A final study visit was performed for patients either after they completed the 4 Treatment Periods or prematurely discontinued from the study.

Patients completed assessments of psychomotor function (approximately 5 min total duration), including the paper-and-pen-
The prospectively defined primary efficacy endpoint was WTDS. Other PSG efficacy variables included WASO, sleep efficiency (SE), TST, LPS, number of awakenings after sleep onset (NAASO), wake time after sleep (WTAS), and sleep architecture. Sleep architecture included the percentages and duration (in min) of Stage 1, 2, and 3/4 sleep, REM sleep, and latency to REM sleep. SE was additionally analyzed by third-of-the-night and by hour of the night in order to further define the sleep maintenance properties of doxepin. Patient-reported measures included LSO, sWASO, sTST, sNAASO and sleep quality (scale from -3 to 3; -3=extremely poor, -2=very poor, -1=poor, 0=fair, 1=good, 2=very good, 3=excellent). Residual next-day sedative effects were assessed objectively with the DSST and the SCT, and subjectively with a 100 mm VAS assessing sleepiness. Safety was evaluated through the monitoring of adverse events at each visit including the final study day. ECG, laboratory testing, and physical examinations were done at screening and on the final study day.

Statistical Analysis

The prospectively defined Per Protocol analysis set was the primary efficacy analysis set for these data; this dataset included all randomized patients who did not have important protocol deviations that would likely have affected the evaluation of efficacy, and who provided WTDS data from each of the 4 Treatment Periods. The intent-to-treat (ITT) analysis set, however, was used to summarize the results in this manuscript; this dataset included all randomized patients who had data from any of the 4 Treatment Periods. Results were consistent between the ITT and Per Protocol analysis sets. Data were analyzed using a repeated-measures analysis of variance (ANOVA) model with terms for sequence, patient within sequence, treatment period, and the Night of the intervention. Prior to the patient leaving the sleep center, assessments of efficacy, concomitant medications, and vital signs were performed.

RESULTS

Study Population

Sixty-seven patients were enrolled and 66 (98.5%) completed this study. The mean age of enrolled patients was 42.4 [standard deviation (SD) = 12.0] years, and the study included more women (70%) than men (30%). Nearly half of the patients were Caucasian (45%), followed by African American (31%), Hispanic (22%) and Asian (1%). At screening, the mean LPS across all patients was 52.5 (23.4) min, mean WTDS was 88.0 (23.6) min, and mean TST was 339.5 (31.0) min.

Sleep Onset, Maintenance, and Duration

PSG Data

WTDS, the primary efficacy endpoint, was statistically significantly reduced at the doxepin 3 mg (P <0.0001) and 6 mg (P <0.0001) doses compared with placebo. WTDS was not statistically significantly reduced at the doxepin 1 mg dose (P = 0.0918) compared with placebo (Table 1). WASO was statistically significantly decreased at all 3 doxepin doses (1 mg, P = 0.0090; 3 mg, P <0.0001; and 6 mg, P <0.0001) compared with placebo. For NAASO, there were no significant differences at any dose of doxepin compared with placebo. LPS was not statistically significantly different from placebo for any doses of doxepin using the a priori defined method of log-transformation (log then average data prior analyses were then performed on these data. Given that there is no consensus on the appropriate process for log-transformation, an alternate post hoc method was also incorporated; this method consisted of averaging the values from Nights 1 and 2 prior to log-transforming the data.

For the DSST, SCT, and VAS, changes from Night 1 (pre-dose) to the average of the Day 2 and Day 3 morning evaluations are presented. The mean changes from Night 1 to the average of the Day 2 and Day 3 value were compared among treatments using an analysis of covariance (ANCOVA) model with terms for sequence, patient within sequence, treatment period, and the Night 1 value as a covariate. Pairwise comparisons of each active treatment versus placebo using Dunnett test were performed.
to analysis). Results were slightly different when data were averaged prior to log-transformation, with statistically significant differences at the 6 mg dose (P = 0.0139) compared with placebo. In terms of sleep duration, TST and overall SE were statistically significantly increased at all 3 doxepin doses (all P-values ≤ 0.0005) compared with placebo. In terms of PSG signs associated with final early morning awakenings (terminal insomnia), WTAS was statistically significantly reduced at the doxepin 6 mg dose (P = 0.0088) compared with placebo, but was not significantly different at the 1 mg (P = 0.1421) and 3 mg doses (P = 0.0697).

SE was additionally analyzed by third-of-the-night (Figure 1). During the first third-of-the-night, SE was statistically significantly increased at the doxepin 3 mg (79.3%, P = 0.0034) and 6 mg (80.1%, P = 0.0002) doses compared with placebo (74.8%). During the second third-of-the-night, SE was statistically significantly increased at the doxepin 6 mg (92.1%, P = 0.0398) dose compared with placebo (89.2%). SE was not statistically significantly increased at the doxepin 1 mg (90.2%, P = 0.8847) and 3 mg doses (92.1%, P = 0.0656) during the second third-of-the-night. During the final third-of-the-night, SE was statistically significantly increased at all 3 doses (1 mg 86.8%, P < 0.0001; 3 mg 88.2%, P < 0.0001; and 6 mg 89.3%, P < 0.0001) compared with placebo (79.6%).

Exploratory post hoc analyses were conducted for SE at each hour (Figure 2). All 3 doxepin doses increased SE at each hour throughout the night compared with placebo, with statistically significantly increased SE at several time points with the 3 and 6 mg doses. All 3 doxepin doses produced statistically significantly increased SE during hour 7 (all P-values ≤ 0.0003) and hour 8 (all P-values ≤ 0.0014), compared with placebo.

Table 1—Polysomnographic Sleep Measures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (N=66)</th>
<th>Doxepin 1 mg (N=66)</th>
<th>Doxepin 3 mg (N=66)</th>
<th>Doxepin 6 mg (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WTDS Mean (SD)</td>
<td>51.5 (40.97)</td>
<td>42.8 (27.48)</td>
<td>34.0 (21.87)</td>
<td>35.8 (24.27)</td>
</tr>
<tr>
<td>WTDS P-value</td>
<td>0.0918</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WASO Mean (SD)</td>
<td>61.1 (45.79)</td>
<td>46.7 (30.01)</td>
<td>38.9 (26.29)</td>
<td>38.1 (25.16)</td>
</tr>
<tr>
<td>WASO P-value</td>
<td>0.0090</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NAASO Mean (SD)</td>
<td>8.7 (3.86)</td>
<td>9.6 (4.39)</td>
<td>8.9 (4.10)</td>
<td>9.0 (4.10)</td>
</tr>
<tr>
<td>NAASO P-value</td>
<td>0.0921</td>
<td>0.9094</td>
<td>0.0677</td>
<td>0.7666</td>
</tr>
<tr>
<td>LPS Mean (SD)</td>
<td>33.0 (22.02)</td>
<td>29.6 (21.71)</td>
<td>30.1 (20.72)</td>
<td>27.3 (19.44)</td>
</tr>
<tr>
<td>LPS P-value&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.2783</td>
<td>0.3829</td>
<td>0.1986</td>
<td>0.1001</td>
</tr>
<tr>
<td>LPS P-value&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.0677</td>
<td>0.1986</td>
<td>0.0139</td>
<td>0.0139</td>
</tr>
<tr>
<td>TST Mean (SD)</td>
<td>389.6 (48.86)</td>
<td>407.5 (35.82)</td>
<td>415.4 (34.50)</td>
<td>418.4 (32.03)</td>
</tr>
<tr>
<td>TST P-value</td>
<td>0.0005</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SE Mean (SD)</td>
<td>81.2 (10.18)</td>
<td>84.9 (7.46)</td>
<td>86.5 (7.19)</td>
<td>87.2 (6.67)</td>
</tr>
<tr>
<td>SE P-value</td>
<td>0.0005</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WTAS Mean (SD)</td>
<td>9.6 (21.04)</td>
<td>3.9 (10.62)</td>
<td>4.9 (16.22)</td>
<td>2.3 (6.21)</td>
</tr>
<tr>
<td>WTAS P-value</td>
<td>0.1522</td>
<td>0.0876</td>
<td>0.0088</td>
<td></td>
</tr>
</tbody>
</table>

Note: P-values reflect comparison of active dose with placebo using Dunnett’s test; WTDS: wake time during sleep; WASO: wake time after sleep onset; NAASO: number of awakenings after sleep onset; LPS: latency to persistent sleep; TST: total sleep time; SE: sleep efficiency; WTAS: wake time after sleep.

*Data were log-transformed prior to analysis; <sup>1</sup>P-value reflects analysis of data that were log-transformed prior to averaging data from Nights 1 and 2; <sup>2</sup>P-value reflects post hoc analysis of data that were averaged prior to log-transformation.

Patient-Reported Data

sWASO was not significantly decreased at the 1 mg (56.4; P = 0.8915), 3 mg (49.4; P = 0.8789), or 6 mg doses (45.1; P = 0.1168) compared with placebo (54.4). sNAASO was statistically significantly decreased at the doxepin 3 mg dose (2.8; P = 0.0207) compared with placebo (3.2). LSO was statistically significantly decreased at the doxepin 6 mg dose (43.0; P = 0.0244), but not significantly decreased at the 1 mg (46.5; P = 0.1944) and 3 mg doses (45.3; P = 0.0905) compared with placebo (49.6) using the a priori defined method of log-transformation (log then average data prior to analysis). Results were slightly different when data were averaged prior to log-transformation, with statistically significant differences at the 3 mg (P = 0.0431) and 6 mg doses (P = 0.0162) compared with placebo. sTST was statistically significantly increased at the doxepin 6 mg (380.7; P = 0.0190) dose, but not significantly increased at the doxepin 1 mg (364.8; P = 0.9992) or 3 mg (380.0; P = 0.0562) doses compared with placebo (364.2). Sleep quality was statistically significantly improved for the doxepin 6 mg dose (0.8; P = 0.0071) compared with placebo (0.4).

Sleep Architecture

There were no statistically significant differences among doses for either percentage or min of Stage 1 sleep. There was a statistically significant increase in percentage of Stage 2 sleep (57.8% at the 3 mg dose level, P = 0.0003; 58.7% at the 6 mg dose, P <0.0001; 54.7% for placebo), a statistically significant increase in min of Stage 2 sleep (228.5 min at the 1 mg doxepin dose level, P
SLEEP, Vol. 30, No. 11, 2007

= 0.0008; 240.4 min at the 3 mg dose, P <0.0001; 245.8 min at the doxepin 6 mg dose level, P <0.0001; and 212.9 min for placebo), and a statistically significant decrease in percentage of REM sleep (18.3% at the 3 mg dose, P = 0.0046; 17.8% at the 6 mg dose, P = 0.0002; and 20.0% for placebo). The number of min spent in REM sleep was not statistically significantly different among doses. There were no statistically significant differences among doses for either percentage or min of Stage 3/4 sleep.

Residual Sedation

There were no statistically significant differences between placebo and any dose of doxepin on any of the measures assessing either psychomotor function (DSST and SCT; Table 2) or next-day alertness (VAS).

Safety

The safety of doxepin at each dose was similar to that of placebo. There was a low incidence of adverse effects (AEs) reported during the conduct of the study. The incidence rates of AEs appeared to be evenly distributed across treatment groups (including placebo) and did not appear to be dose related. Table 3 summarizes all adverse events occurring in more than 2% of patients. Six patients (9%) experienced ≥1 AE during the placebo treatment period, 9 patients (14%) during the doxepin 1 mg treatment together.

![Figure 1](image-url)
period, 5 patients (8%) during the doxepin 3 mg treatment period, and 8 patients (12%) during the doxepin 6 mg treatment period. The numbers of patients reporting events, as well as the number of events, were similar across treatments. The only AEs reported by >2% of patients were headache and somnolence. All reported AEs were either mild or moderate in severity and there were no serious adverse events. One patient (1%) discontinued the study due to an adverse event of anxiety after receipt of the first dose of study drug (doxepin 6 mg; considered possibly related to study drug). No treatment was required and symptoms were resolved on the day of onset with no sequelae. There were no clinically relevant changes in laboratory parameters, vital signs, physical examinations, or ECGs.

DISCUSSION

In this randomized, placebo-controlled, crossover study of adults with primary insomnia, doxepin at doses of 1 mg, 3 mg, and 6 mg produced improvement in PSG-defined and patient-reported sleep maintenance and duration endpoints that persisted through the final third-of-the-night. These improvements were evidenced by significant changes in WASO, TST, and overall SE for all doses versus placebo. Additionally, the primary study endpoint, WTDS, was significantly decreased at the doxepin 3 mg and 6 mg doses, compared with placebo. The doxepin 1 mg, 3 mg, and 6 mg doses not only significantly improved the traditional sleep maintenance parameters but also appeared to significantly reduce the PSG signs associated with early morning awakenings (i.e., terminal insomnia), including significant reductions to WTAS (6 mg only), SE in the final third-of-the-night and SE in hours 7 and 8. Though numeric improvements in sleep onset were observed, statistical significance was seen only at the 6 mg dose. In general, the subjective sleep efficacy data were directionally consistent with the PSG results, though the sleep-promoting effects were clearly more robust in the PSG data. There were no significant group differences in next-day residual sedation. All 3 doses of doxepin were well tolerated with a low incidence of adverse events, comparable to that observed during the placebo treatment period. In addition, though there were small, statistically significant changes to Stage 2 and REM sleep, sleep architecture was generally clinically preserved.

In the current study, although sleep was generally improved for all three doxepin doses, the effect was stronger for 3 mg and 6 mg. Further, the quantitative similarity between the 3 mg and 6 mg doses suggests an asymptote for the hypnotic activity of doxepin at this dose range. The PSG sleep maintenance improvements observed for these doses were both statistically significant and clinically important. For example, doxepin 3 mg and 6 mg improved WASO by approximately 23 min, with a 25- to 29-min improvement in TST, all relative to the placebo group. Doxepin 3 mg and 6 mg significantly improved SE during the first two thirds-of-the-night, with significant improvement in all doses during the final third-of-the-night. In addition to these improvements, doxepin 1 mg and 3 mg numerically improved WTAS, doxepin 6 mg significantly improved WTAS, and all 3 doses significantly improved SE at hours 7 and 8, suggesting that doxepin also reduced the PSG signs associated with early morning awakenings. These data indicate that the sleep maintenance improvements produced by 3 mg and 6 mg were substantial and were sustained throughout the night. It is interesting to note that doxepin demonstrated sleep effects lasting into the final third of the night without being associated with significant next-day residual sedation (relative to placebo) or other adverse side effects; none of the available hypnotic agents have any published data demonstrating this effect.5,17 This unexpected finding of improvements to the PSG signs associated with early morning awakenings suggest that future work with low doses of doxepin is warranted assessing patients specifically reporting early morning awakenings.

The present study and previous research demonstrate that doxepin consistently improves sleep maintenance and sleep duration, even at doses as low as 1 mg.12-14 There was, however, distinction in the present study. Patients taking doxepin 1 mg, 3 mg, and 6 mg did not spontaneously report the well-documented anticholinergic and other adverse effects that are commonly associated with doxepin use at higher doses (e.g., doxepin 75 and 150 mg;11 doxepin 25-50 mg14). However, given that adverse effects were only assessed across 2 nights for each dose, it is premature to conclude that these doses of doxepin would not result in anticholinergic effects with longer exposure.

Although sleep was consistently improved in the present study, a potential limitation of these data is that efficacy was only evaluated across 2 nights, and thus no conclusion about the sustainability of these results can be made from this study. Additionally, no conclusion about the potential for withdrawal effects after doxepin use can be made from this study.

In the present study, the low incidence of adverse effects combined with the apparent absence of significant residual sedation (based on the measures used in this study, compared with placebo) in the presence of consistent sleep maintenance improvements throughout the night warrants further discussion. In contrast to the hypnotic agents that target the GABA receptor complex, the hypothesized mechanism of action (MOA) for the effects of these low doses of doxepin on sleep are thought to be mediated by the histaminergic system. There are several different strands of evidence supporting this theory. Doxepin is a highly potent histamine (predominantly H1) antagonist, with a sub-nanomolar affinity approximately 7 times greater than mepyramine, the classical H1 antagonist and reference compound.18 Further, there is evidence in both animals and humans that histamine release is a key element in maintaining wakefulness.19,20 and that the H1 receptor may be the primary histaminergic mediator of arousal and the sleep-wake cycle.21-24 Given this relationship between H1 receptors and the sleep/wake cycle, and the antagonist potency of doxepin at the H1 receptor, it is likely that the blockade of H1 receptors reduces wakefulness, thus promoting sleep and preventing histaminergic disruption of sleep.

Although this theory helps explain the consistent sleep improvements, the apparent absence of next-day residual sedation in this study and the pattern of histamine fluctuation through

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**Table 3**—Summary of Adverse Events (% reported in more than 2% of patients at any dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>Doxepin 1 mg</th>
<th>Doxepin 3 mg</th>
<th>Doxepin 6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>9%</td>
<td>14%</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0%</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>
the 24-hour day suggest that time of day may also be an important variable. Further refinement of this theory suggests that at the point in the circadian cycle when the endogenous drive for sleep is at its greatest and when the release of histamine and wakefulness are naturally reduced, the blockage of histamine can further reduce wake drive and thus promote sleep. Conversely, as the drive for wakefulness and the circadian release of histamine increase rapidly in the morning in concert with a low sleep drive, the histaminergic blockade is overcome, and awakening occurs with little to no residual sedation. Although sleep/wake function is governed by several distinct and complex systems, many of which we have not elaborated upon, the aforementioned results at these doses may be due in part to a combination of the potency/selectivity of doxepin at these doses for histaminergic receptors (specifically H1), and the effects of the endogenous opponent processes that are theorized to influence the sleep-wake cycle.25

In conclusion, doxepin 1 mg, 3 mg, and 6 mg produced improvement in PSG-defined and patient-reported sleep maintenance and duration endpoints that persisted throughout the night (including the final third-of-the-night) in adults with primary insomnia. Effects on sleep onset (LSO at 6 mg) and early morning awakenings also were observed at the higher doses. In terms of safety, the AE profile was comparable to placebo; there were no reported anticholinergic effects, there were no significant hangover/next-day residual effects compared with placebo, and sleep architecture was generally clinically preserved.

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