Efficacy and Safety of Doxepin 1 mg, 3 mg, and 6 mg in Elderly Patients With Primary Insomnia: A Randomized, Double-Blind, Placebo-Controlled Crossover Study

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Objectives: Evaluate efficacy and safety of the histamine-H$_1$ antagonist doxepin at doses of 1 mg, 3 mg, and 6 mg in elderly adults with primary insomnia.

Design: A randomized, double-blind, placebo-controlled, crossover design was used in this population of elderly adults with primary insomnia (DSM-IV). Each treatment period consisted of 2 polysomnographic (PSG) assessment nights with a 5- or 12-day drug-free interval between periods. The study was conducted from September 2004 to January 2005.

Setting: Sleep laboratories in 11 sleep centers in the United States.

Participants: Elderly adults with primary insomnia.

Intervention: Doxepin 1 mg, 3 mg, and 6 mg.

Measurements: Efficacy was assessed using PSG and patient-reported measures.

Results: Seventy-six patients were randomly assigned. All 3 doxepin doses produced dose-related significant improvements in PSG-determined wake time during sleep (p < .0001), wake time after sleep onset (p < .0001), total sleep time (p < .0001), and overall sleep efficiency (p < .0001) versus placebo. At the 3-mg and 6-mg doses, sleep efficiency was significantly improved during all thirds of the night (p < .05). There was a dose-related decrease in patient-reported sleep latency, with the 6-mg dose achieving statistical significance in latency to sleep onset (p = .0181). The pattern of the remaining subjective efficacy results was consistent with PSG. All 3 doxepin doses had side effect profiles comparable to placebo, with no spontaneously reported anticholinergic effects, no memory impairment, and no significant next-day residual effects.

Conclusions: In this 2-night study of elderly adults with primary insomnia, doxepin doses of 1 mg, 3 mg, and 6 mg were well tolerated and produced significant improvement in objective and subjective sleep maintenance and duration endpoints that persisted into the final hour of the night. Positive effects on patient-reported sleep onset were observed at the highest dose. All 3 doxepin doses had a safety profile comparable to placebo. These data demonstrate that doxepin was efficacious in improving sleep in elderly adults.

(J Clin Psychiatry 2008;69:1557–1564)

Insomnia is diagnosed by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), as a disorder characterized by symptoms of difficulty with sleep initiation, sleep maintenance, or nonrestorative sleep associated with impairments in daily function or daytime distress.[1] Chronic insomnia is the most prevalent sleep disorder in the United States, affecting an estimated 10%–15% of the adult population.[2–4] The prevalence of insomnia is greater in the elderly, with an estimated 20%–30% of elderly adults (≥ 65 years of age) meeting diagnostic criteria for insomnia.[5–8]

The consequences of insomnia can be profound, with disturbed sleep being associated with a number of adverse outcomes including difficulty concentrating, memory impairment, impaired performance, and increased risk of serious falls in the elderly.[9,10] Unfortunately, all of these sequelae may be mistaken for dementia in elderly patients in the clinic, adding a layer of complexity to the diagnosis and management of insomnia in this population.[11]

Although the presence of sleep disturbance in the elderly clearly warrants attention, there are several issues unique to this population that pose challenges for clini-

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cians. Because the elderly frequently have multiple medical conditions, they often must be managed with polypharmacy, thus raising the risk of drug-drug interactions. Additionally, the presence of multiple medical conditions may contribute to sleep disturbance, making it difficult to determine the best treatment regimen. Thus, the diagnostic process and the decision on treatment regimen are more complex in the elderly.

While there is a growing appreciation of the need to focus attention on the treatment of sleep maintenance problems in the elderly, data on the use of sleep agents in this population are limited.[12] To date, there are only 8 large (i.e., N > 50), randomized, placebo-controlled studies published that address hypnotic efficacy in elderly adults with primary insomnia.[13–20] These studies indicate treatment with eszopiclone,[13,14] zaleplon,[15,16] temazepam,[17,18] flurazepam,[17] and ramelteon[19] reduced sleep latency in older adults. The results were inconsistent for zolpidem[16,18] and there was no benefit from tiagabine.[20] Of these agents, only eszopiclone 2 mg demonstrated significant improvement in sleep maintenance parameters.[13,14]

These data suggest that medications currently approved for insomnia may not have consistent sleep maintaining properties in elderly populations. This is important given the emerging consensus among clinicians and sleep specialists that sleep maintenance is a uniquely important therapeutic target in the elderly.[7,21]

Doxepin, a compound with potent histamine blocking activity (mainly H_1), has long been known to have significant sleep promoting effects,[22] with 3 randomized clinical trials examining this effect.[23–25] Efficacy results from these trials indicated that nightly administration of doxepin 25–50 mg significantly improved polysomnographic (PSG) sleep measures versus placebo, including total sleep time (TST) and wake time after sleep onset (WASO).[23–25] However, safety results from these trials suggest that the optimal hypnotic dosages have not been systematically defined. Doxepin at doses ≥ 25 mg is associated with undesirable side effects, including significant anticholinergic effects.[22,25]

The present investigation explored the effects of low doses of doxepin, a compound known to have sedating properties at higher doses, on sleep parameters. It was hypothesized that doxepin would improve sleep maintenance in comparison to placebo, using both objective (PSG) and subjective (patient-reported) outcome measures, without causing significant next-day residual effects.

METHODS

The present study was a randomized, multi-center (11 sleep centers in the United States), double-blind, placebo-controlled, 4-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 elderly patients with chronic primary insomnia. All subjects signed an informed-consent form prior to the screening visit. The study was conducted from September 2004 to January 2005.

Patients

Patients were recruited using a variety of advertising campaigns including the media. Eligible patients were men and women aged 65 and older. One hundred ninety-six patients were screened for study participation. The initial screening was used to verify that all patients had a DSM-IV diagnosis of primary insomnia for at least the last 3 months, a reported total sleep time (sTST) ≤ 6.5 hours, a reported wake time after sleep onset (sWASO) ≥ 60 minutes, and a reported latency to sleep onset (LSO) ≥ 20 minutes, all on at least 4 nights per week. This initial screening process included a structured clinical diagnostic interview, which was used to determine whether the patient had primary insomnia and to rule out insomnia secondary to some other source. Patients were excluded from the study if they reported (1) consuming more than 4 alcoholic beverages in a day or more than 15 alcoholic beverages weekly within the last 14 days before screening; (2) using nicotine-containing products (≥ 15 cigarettes daily) or using nicotine-containing products within 30 minutes of bedtime (including nicotine replacement therapy), during the middle of the night, or within 30 minutes of awakening; (3) consuming more than 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 more than 2 times per week; (5) having a variation in bedtime of more than 2 hours on 5 of 7 nights based on screening sleep diaries; (6) having a history of cognitive disorders, depression, schizophrenia, panic disorder, dementia, chronic pain, glaucoma, or frequent nightly urination (> 2 times per night); (7) testing positive at 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; (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; or (9) using a hypnotic or any other medication known to affect sleep.

Patients meeting the above screening criteria (N = 152) completed 2 consecutive nights of PSG evaluation to determine whether they met PSG screening criteria. Patients were required to have a latency to persistent sleep (LPS) ≥ 10 minutes, a wake time during sleep (WTDS) ≥ 60 minutes with no night < 45 minutes, and a TST > 240 and ≤ 410 minutes in order to be eligible for randomization. The PSG and patient-reported quantitative screening criteria were selected based on an effect size calculation.

Patients were excluded from the study during PSG screening if they had periodic limb movement disorder (≥ 15 periodic limb movements with arousal per hour of sleep) or sleep apnea (≥ 15 apnea/hypopnea events per hour of sleep).

An 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 Harmonization Guideline for Good Clinical Practice.

Procedure

Seventy-six patients met all entry criteria and were randomly assigned to 1 of 4 treatment sequences. Randomization in this 4-period crossover study was done in a 1:1:1:1 ratio using a Latin square design, with all patients receiving all treatments (doxepin 1 mg, 3 mg, and 6 mg and placebo). Each patient completed 5 2-day assessment periods (includes 1 single-blind placebo screening period and 4 double-blind treatment periods) with a 5- or 12-day drug-free interval between treatment periods. The differing interval between periods reflects the leeway patients were given in scheduling their next sleep laboratory visit. During each treatment period, patients received 2 consecutive nights of treatment, each followed by 8 hours of PSG recording in a sleep laboratory. Efficacy assessments were performed 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 occurred for patients either after they completed the 4 treatment periods or prematurely discontinued from the study.

Patients completed assessments of psychomotor function, including the Digit-Symbol Substitution Test (DSST) and the Symbol Copying Test (SCT); patients also completed a visual analog scale (VAS) assessing degree of sleepiness prior to dosing on the first night of each treatment period. Study drug was administered approximately 30 minutes before the patient's median habitual bedtime (lights-out). Following lights-out, PSG measures were recorded for 8 hours.

Each morning at approximately 9 hours after study-drug administration, patients completed a questionnaire assessing sleep efficacy and complete psychomotor function tests. Prior to leaving the sleep center, assessments of adverse events, concomitant medications, and vital signs were performed.

Study Assessments

Polysomnographic recordings were scored centrally in a blinded manner by qualified, trained individuals in accordance with the Rechtschaffen and Kales manual. The prospectively defined primary efficacy endpoint was WTDS. Wake time during sleep is a key measure of sleep maintenance, representing the cumulative time awake from the beginning of persistent sleep to final awakening. Other PSG efficacy variables included WASO, sleep efficiency, 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 minutes) of stage 1, 2, and 3/4 sleep, rapid eye movement (REM) sleep, and latency to REM sleep. Sleep efficiency was further analyzed by third of the night and by hour of the night. 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 SCT and subjectively with a 100 mm VAS assessing sleepiness. Safety was evaluated by adverse events monitored throughout the study. Laboratory testing and physical exams were performed at screening and on the final study day. Electrocardiograms were performed before and after each treatment period.

Statistical Analysis

The prospectively defined per protocol analysis set was the primary efficacy analysis set used to analyze these data. The intent-to-treat analysis set, however, was used to summarize the results in this manuscript; this dataset included all randomly assigned patients who contributed data from any of the 4 treatment periods. Results for the intent-to-treat and per protocol analysis sets were consistent. Data were analyzed using a repeated-measures analysis of variance model with terms for sequence, patient within sequence, treatment, and period. The covariance among the repeated measures was modeled separately as unstructured, compound symmetric, and first-order auto-regressive. The covariance structure corresponding to the model with the smallest Akaike's Information Criterion was selected for use. Pairwise comparisons of each active treatment versus placebo were conducted only if the omnibus test was significant and were performed using Dunnett's test. Measurements taken from nights 1 and 2 from each treatment period were averaged for analysis.

Latency to persistent sleep, latency to REM sleep, and LSO were log-transformed prior to analysis due to the expectation that these variables would be log-normally distributed. The prospectively defined transformation method specified the data were to be log-transformed prior to averaging the values from nights 1 and 2, and statistical analyses were then performed on these data.

For the DSST, SCT, and VAS measures, the average of the day 2 and day 3 morning evaluations were presented. The mean changes from night 1 to the average of the day 2 and day 3 values were compared among treatments using an analysis of covariance model with terms for sequence, patient within sequence, treatment period, and the night 1

Figure 1. Effects of Doxepin on Wake Time After Sleep Onset (WASO) in Elderly Patients With Primary Insomnia[a]
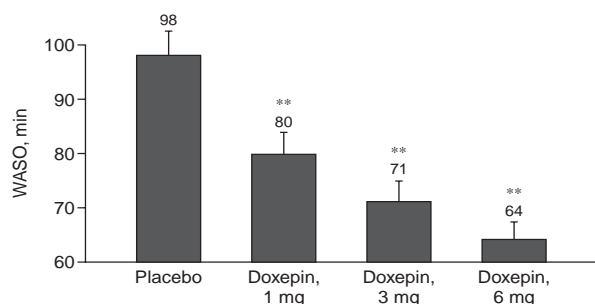
**p < .0001.
[a]Error bars reflect stand error of the mean.

Table 1. Effect of Doxepin and Placebo on Polysomnographic Parameters in Elderly Patients With Primary Insomnia[a]

Parameter	Placebo (N = 73)	Doxepin, 1 mg (N = 74)	Doxepin, 3 mg (N = 74)	Doxepin, 6 mg (N = 74)
WTDS, min				
Mean (SD)	85.8 (38.39)	69.6 (32.61)	64.8 (31.96)	59.5 (28.3)
p Value	…	< .0001	< .0001	< .0001
NAASO				
Mean (SD)	11.9 (4.45)	12.1 (4.98)	12.5 (5.34)	12.5 (4.76)
p Value	…	.8591	.2536	.2346
LPS, min[b]				
Mean (SD)	26.8 (19.29)	28.0 (21.01)	23.2 (17.21)	22.4 (14.04)
p Value	…	.9811	.0667	.2486
TST, min				
Mean (SD)	360.7 (43.98)	377.4 (37.63)	390.6 (41.02)	398.4 (32.29)
p Value	…	< .0001	< .0001	< .0001
Sleep efficiency, %				
Mean (SD)	75.1 (9.16)	78.6 (7.84)	81.4 (8.54)	83.0 (6.73)
p Value	…	< .0001	< .0001	< .0001
WTAS, min				
Mean (SD)	12.2 (16.97)	10.5 (15.99)	6.0 (9.88)	4.8 (7.91)
p Value	…	.5973	.0197	.0005

[a]p Values reflect comparison of active dose with placebo using Dunnett's test.
[b]Data were log-transformed prior to analysis; pretransformed values are presented here.
Abbreviations: LPS = latency to persistent sleep, NAASO = number of awakenings after sleep onset, TST = total sleep time, WTAS = wake time after sleep, WTDS = wake time during sleep.

Figure 2. Effects of Doxepin on Sleep Efficiency by Third of the Night[a]
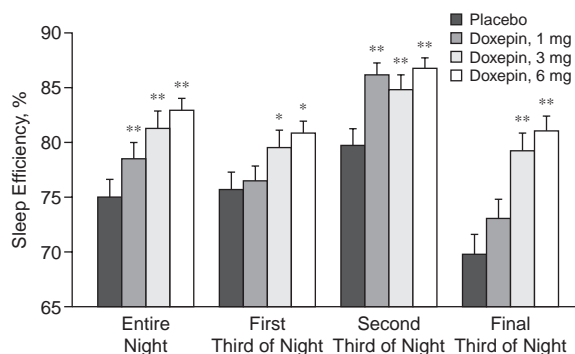
*p < .05.
**p < .0001.
[a]Error bars reflect stand error of the mean.

value as a covariate. Pairwise comparisons of each active treatment versus placebo using Dunnett's test were performed.

RESULTS

Study Population

Seventy-six patients were enrolled and 73 (96.1%) completed this study. The mean age of enrolled patients was 71.0 years [standard deviation (SD) = 4.8], and the study included more women (61%, N = 46) than men (39%, N = 30). Most of the patients were white (86%, N = 65), followed by African American (11%, N = 8), Hispanic (3%, N = 2), and Asian (1%, N = 1). At screening, mean (SD) LPS across all patients was 38.4 (23.5) minutes, mean (SD) WTDS was 96.1 (28.5) minutes, and mean (SD) TST was 340.8 (38.6) minutes.

Sleep Onset, Maintenance, and Duration

PSG endpoints. Wake time during sleep, the primary efficacy endpoint, and the related endpoint WASO (Figure 1) were significantly reduced at all doxepin doses (all p values < .0001) compared with placebo (Table 1). There were no significant differences for NAASO for any dose of doxepin compared to placebo. Latency to persistent sleep was not significantly different from placebo for any dose of doxepin. Total sleep time and overall sleep efficiency were significantly increased at all 3 doxepin doses (all p values < .0001) compared with placebo. Wake time after sleep was significantly reduced at the doxepin 3-mg (p = .0197) and 6-mg doses (p = .0005) compared with placebo.

Sleep efficiency was further analyzed by each third of the night (Figure 2). During the first third of the night, sleep efficiency was significantly increased at the doxepin 3-mg (p = .0369) and 6-mg (p = .0020) doses compared with placebo. During the second third of the night, sleep efficiency was significantly increased at all 3 doses (all p values < .0001) compared with placebo. During the final third of the night, sleep efficiency was significantly increased at the 3-mg and 6-mg doses (both p values < .0001) compared with placebo. Sleep efficiency was numerically but not significantly increased at the doxepin 1-mg dose (p = .0867) during the final third of the night.

Post hoc analyses were conducted for sleep efficiency by hour of the night (Figure 3).

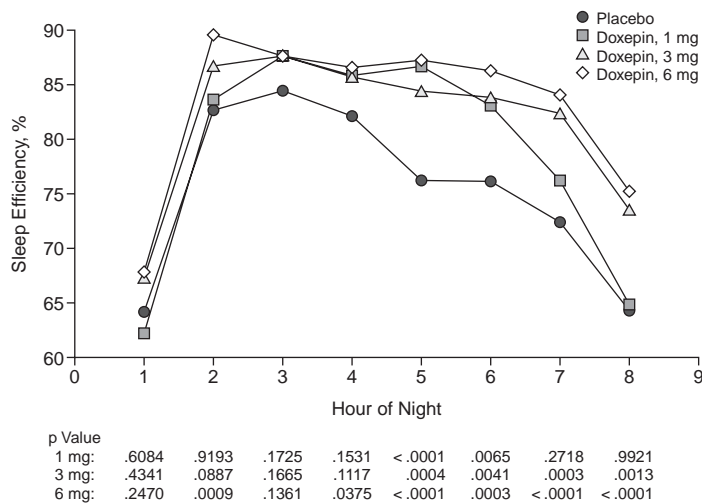Figure 3. Effects of Doxepin on Sleep Efficiency by Hour of the Night

p Value								
1 mg:	.6084	.9193	.1725	.1531	< .0001	.0065	.2718	.9921
3 mg:	.4341	.0887	.1665	.1117	.0004	.0041	.0003	.0013
6 mg:	.2470	.0009	.1361	.0375	< .0001	.0003	< .0001	< .0001

Table 2. Effect of Doxepin and Placebo on Subjective Parameters[a]

Parameter	Placebo (N = 73)	Doxepin, 1 mg (N = 74)	Doxepin, 3 mg (N = 74)	Doxepin, 6 mg (N = 74)
sWASO, min				
Mean (SD)	89.3 (61.56)	74.1 (55.42)	69.3 (56.31)	70.2 (57.08)
p Value	…	.0277	.0034	.0024
sNAASO				
Mean (SD)	3.2 (1.58)	3.2 (2.08)	2.8 (1.73)	2.9 (1.45)
p Value	…	.9849	.1457	.1793
LSO, min[b]				
Mean (SD)	45.5 (35.48)	42.4 (31.54)	42.7 (39.86)	33.8 (24.36)
p Value	…	.9995	.3238	.0181
sTST, min				
Mean (SD)	340.0 (71.79)	356.6 (63.06)	364.2 (64.90)	370.8 (64.59)
p Value	…	.0112	.0002	< .0001
Sleep quality[c]				
Mean (SD)	0.5 (0.99)	0.7 (0.95)	0.9 (0.93)	0.9 (0.92)
p Value	…	.0381	.0003	.0017

[a]p Values reflect comparison of active dose with placebo using Dunnett's test.
[b]Data were log-transformed prior to analysis; pretransformed values are presented here.
[c]Sleep quality: −3 = extremely poor, −2 = very poor, −1 = poor, 0 = fair, 1 = good, 2 = very good, 3 = excellent.
Abbreviations: LSO = latency to sleep onset, sNAASO = subjective number of awakenings after sleep onset, sTST = subjective total sleep time, sWASO = subjective wake time after sleep onset.

With the exception of the hour 1 value for doxepin 1 mg, all 3 doxepin doses had numerically improved sleep efficiency at each hour throughout the night compared with placebo. At the doxepin 6-mg dose, sleep efficiency was statistically significantly increased at hours 2, 4, 5, 6, 7, and 8. At the doxepin 3-mg dose, sleep efficiency was statistically significantly increased at hours 5, 6, 7, and 8. At the 1-mg dose, sleep efficiency was statistically significantly increased at hours 5 and 6.

Patient-reported data. Reported wake time after sleep onset was significantly decreased at all doxepin doses (all p values < .05) compared with placebo (Table 2).

There were no significant differences in sNAASO across any doxepin dose compared with placebo. Latency to sleep onset was significantly decreased at the doxepin 6-mg dose (p = .0181) and numerically decreased at the 1-mg and 3-mg doses compared with placebo. Both sTST and sleep quality were significantly increased at all doxepin doses (all p values < .05) compared with placebo.

Sleep Architecture

Sleep stages were generally preserved in the doxepin-treated groups (Figure 4). There was a significant increase in percentage (12.7% for placebo; 13.6% at the 6-mg dose, p = .0279) and duration of stage 1 sleep (45.2 minutes for placebo; 51.6 minutes at the doxepin 3-mg dose, p < .0001; 53.6 minutes at the doxepin 6-mg dose, p < .0001) compared with placebo. There was a significant increase in percentage (53.0% for placebo; 55.0% at the 3-mg dose, p = .0123; 56.2% at the 6-mg dose, p < .0001) and duration of stage 2 sleep (190.5 minutes for placebo; 202.7 minutes at the 1-mg doxepin dose, p = .0034; 214.1 minutes at the doxepin 3-mg dose, p < .0001; 223.0 minutes at the doxepin 6-mg dose, p < .0001) compared with placebo. There were no statistically significant changes to percentage or duration of stage 3/4 sleep. There was a significant decrease in percentage (19.7% for placebo; 17.8% at the 1-mg doxepin dose, p = .0004; 16.7% at the 3-mg dose, p < .0001; 16.1% at the 6-mg dose, p < .0001) and duration of REM sleep (72.1 minutes for placebo; 65.7 minutes at the doxepin 3-mg dose, p = .0205; 64.7 minutes at the doxepin 6-mg dose, p = .0003), compared with placebo. Finally, there was a significant increase in latency to REM sleep at the 6-mg dose (87.7 minutes, p = .0285) compared with placebo (68.7 minutes).

Residual Psychomotor Impairment

There were no significant differences between placebo and any dose of doxepin on any measure assessing psychomotor function (DSST and SCT) or next-day sleepiness (VAS), as shown in Table 3.

Safety

Overall, 32 adverse events (AEs) were reported during the conduct of the study. The only AE reported by more than 1 patient was headache, occurring in 2 patients (3%) during the placebo treatment period. The incidence rates of AEs did not appear to be dose-related. The numbers of

Figure 4. Effects of Doxepin 1 mg, 3 mg, and 6 mg on Sleep Stages: Mean Number of Minutes in Each Sleep Stage on Night 1
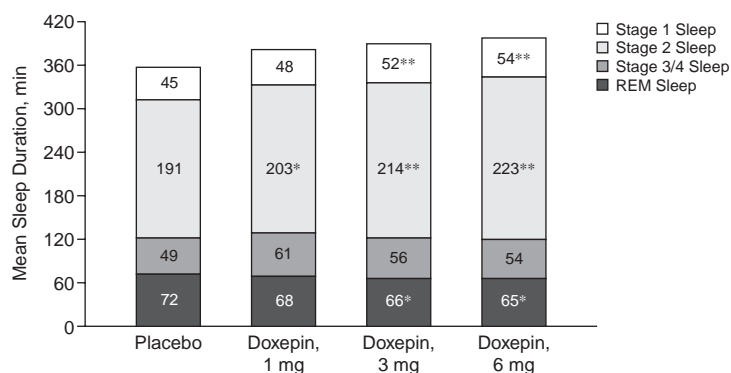
*p < .05.
**p < .0001.
Abbreviation: REM = rapid eye movement.

Table 3. Next-Day Psychomotor Residual Effects[a]

Parameter	Placebo (N = 73)	Doxepin, 1 mg (N = 74)	Doxepin, 3 mg (N = 74)	Doxepin, 6 mg (N = 74)
DSST				
Mean (SD)	52.4 (11.7)	52.5 (11.2)	52.1 (11.5)	52.2 (12.1)
p Value	…	1.0000	1.0000	.9885
SCT				
Mean (SD)	96.0 (21.5)	96.1 (20.3)	95.0 (20.7)	95.4 (21.9)
p Value	…	.9340	.3123	.2925
VAS[b]				
Mean (SD)	63.3 (19.3)	64.4 (18.6)	62.3 (18.4)	62.9 (19.9)
p Value	…	.8228	.9141	.9746

[a]p Value for testing each doxepin dose versus placebo was determined from an analysis of covariance model with terms for treatment and center and the night 1 value as a covariate using a linear contrast; scores represent the average of day 2 and day 3.
[b]Visual analog scale (VAS) for sleepiness is inverted for consistency with DSST and SCT results.
Abbreviations: DSST = digit-symbol substitution test, SCT = symbol copying test.

patients reporting AEs, as well as the number of AEs, were similar across treatments. Seven patients (10%) experienced at least 1 AE during the placebo treatment period, 9 patients (12%) during the doxepin 1-mg treatment period, 6 patients (8%) during the doxepin 3-mg treatment period, and 5 patients (7%) during the doxepin 6-mg treatment period. All reported AEs were either mild or moderate in severity except for 1 serious AE of chest pain that required hospitalization (occurred during doxepin 1-mg treatment and was moderate in intensity). The pain, which resolved the day after onset, was determined to be unrelated to study drug and noncardiac in origin. There were no clinically relevant changes in laboratory parameters, vital signs, physical examinations, or electrocardiograms.

DISCUSSION

In this randomized, placebo-controlled, 2-night crossover study of elderly 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 throughout the entire night, including the final hour of the night. These improvements were evidenced by statistically significant changes in the PSG variables WTDS (primary study endpoint), WASO, TST, and overall sleep efficiency for all doses versus placebo. The doxepin 3-mg and 6-mg doses also significantly reduced PSG-defined WTAS and increased sleep efficiency at hours 7 and 8, suggesting that these doses prevented early morning awakenings. Improvements in sleep onset were observed, with statistical significance at the highest dose of the patient-reported data (6 mg for LSO). The patient-reported efficacy data were consistent with the PSG results. Next-day measures of residual effects revealed no evidence of impairment by doxepin relative to placebo on either objective (DSST and SCT) or patient-reported measurements (VAS). All 3 doxepin doses were well tolerated, with a low incidence of adverse events comparable to that observed during the placebo treatment period.

These findings are consistent with results from other trials in nonelderly adults assessing the sleep efficacy of doxepin at doses ≤ 6 mg.[26,27] One of these trials assessed the efficacy and safety of doxepin 3 mg and 6 mg in a 35-day randomized, double-blind, parallel-group trial,[26] while the other assessed the efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in a 2-night randomized, double-blind crossover trial.[27] Results of these studies indicated doxepin at these low doses was well tolerated and produced statistically significant and clinically relevant improvement in objective and subjective sleep maintenance and duration endpoints that persisted into the final hour of the night.[26,27] Additionally, doxepin 3 mg and 6 mg demonstrated a statistically significant reduction in LPS in 1 of these trials[26] and appeared to reduce the duration of early morning awakenings in both.[26,27] The adverse event profile in both studies was comparable to placebo, with no spontaneously reported anticholinergic effects (e.g., dry mouth, blurred vision), no memory impairment, and no significant hangover/next-day residual effects.

In the present study, the significant improvement in sleep maintenance across all doses was accompanied by significant improvements in WTAS and sleep efficiency at hours 7 and 8 in the 3-mg and 6-mg dose groups. These data suggest that doxepin reduces the duration of and may prevent early awakenings, a novel finding in the insomnia treatment literature for a drug with no observed next-day

residual effects. The improvements in sleep throughout the night are particularly noteworthy for the elderly population. Sleep maintenance problems, broadly defined as the inability to stay asleep throughout the night, predominate in this population. The most frequently reported symptoms of sleep disturbance in the elderly are extended nocturnal awakenings and waking up too early in the morning and being unable to return back to sleep, with the latter often referred to as early morning awakenings.[5,8] The inability to sleep throughout the night has been associated with deleterious consequences such as decreased quality of life.[28,29] Sleep maintenance dysfunction has also been associated with daytime fatigue.[30] Therefore, obtaining uninterrupted sleep throughout the night is a critical aspect of insomnia treatment and is an important objective in the elderly population.

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. Further, given that adverse effects were also only assessed across 2 nights for each dose, it may be premature to conclude that these doses of doxepin would not result in anticholinergic effects or memory impairment with longer exposure.

The effects of doxepin 1 mg, 3 mg, and 6 mg on sleep in the present study are thought to be mediated through the histaminergic system. Histamine mediates sleep/wake aspects of the circadian rhythm by exciting systems that promote wakefulness/arousal at appropriate times in the 24-hour cycle.[31,32] At the doses used in this study, doxepin appears to be a selective histamine H_1 antagonist due to the high selectivity of this receptor versus other known targets such as receptors mediating adrenergic or serotonergic activity.

This histamine antagonist method of promoting sleep differs from hypnotic agents that target the γ-aminobutyric acid (GABA) receptor complex. Crucial differences from GABA agonist approaches to insomnia include (1) doxepin is essentially inactive at the benzodiazepine receptor[33]; (2) histamine activity fluctuates over the circadian cycle and is greatest in the latter part of the night and early morning, when it facilitates the natural transition from sleep to waking[34]; and (3) sleep-enhancement involves antagonism of histamine and has the effect of preventing sleep-disturbing arousal at times of natural vulnerability such as in the middle of the night and early morning. Additionally, unlike the diffuse effects that occur after stimulation of GABA, these low doses of doxepin appear to selectively affect histamine. Thus, in the morning when other systems exert an independent influence on wakefulness (e.g., orexin), doxepin would not interfere with those effects.

In conclusion, 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 throughout the night (including the final third of the night) in elderly patients with primary insomnia in this short-term study. Positive effects on initiating sleep onset and reducing the duration of early morning awakenings also were observed at the higher doses. In terms of safety, the adverse event profile was comparable to placebo, there were no spontaneously reported anticholinergic effects, and there were no measurable hangover/next-day residual effects across the 2-night treatment period.

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