Doxepin (Silenor)

National Drug Monograph

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary[1-4]

Silenor (doxepin) is a tricyclic antidepressant. It inhibits the reuptake of serotonin and norepinephrine and possesses cholinergic, histaminergic, and alpha 1-adrenergic receptor blockade activities. At low doses (≤ 6 mg), it has high affinity and selectivity for the H_1 histamine receptors. By selectively blocking the histamine receptors, doxepin prevents histaminergic mediator of arousal and the sleep-wake cycle thus, it reduces wakefulness and instead, promotes sleep.

Indication:[1,2]

Low dose doxepin (3 mg and 6 mg) received FDA approval in March, 2010 for the treatment of insomnia characterized by difficulty with sleep maintenance. Sleep maintenance difficulty is characterized by the inability to remain asleep throughout the night or the propensity for early morning awakenings.

Efficacy:

Efficacy for improving sleep maintenance has been supported by six industry sponsored randomized, double-blind studies (longest duration being 3 months) which included 1,423 subjects, 18-93 years of age with chronic (n=858) or induced transient (n=565) insomnia. Doses evaluated were1 mg, 3 mg, and 6 mg compared to placebo in sleep laboratory and outpatient settings. The primary efficacy measures for assessing sleep maintenance are objective and subjective Wake After Sleep Onset (WASO, sWASO), respectively, as well as total sleep time (TST), subjective total sleep time (sTST), and sleep efficiency (SE).

Chronic Insomnia: Adults

Two randomized, double-blind, placebo-controlled studies[5, 6] evaluated the efficacy of low dose doxepin (DXP) compared to placebo in adult patients with primary insomnia. Krystal et al.[5] (2011) evaluated adults (n=221) using 3 mg and 6 mg DXP for 35 consecutive nights using objective and subjective assessments. The primary endpoint was WASO on Night 1 (N1). Mean WASO significantly decreased with DXP 3 mg by 25.4 minutes ($p \leq 0.0001$) and 6 mg by 30.5 minutes ($p \leq 0.0001$), compared to placebo. Other sleep maintenance measures (TST, sWASO, sTST, and SE in Last Quarter of Night, %) also improved in both study groups on N1 and N29 compared to placebo. (Refer to Appendix A-Table 1 for further details.)

Roth et al.[6] randomized 67 adults (18-64 years) with chronic primary insomnia to 1 mg, 3 mg, and 6 mg DXP and placebo in a double-blind four-period crossover study consisting of 2 polysomnographic (PSG) assessment nights and patient-reported measures. Wake Time During Sleep (WTDS) was the primary endpoint. The WTDS was reduced significantly with DXP 3 mg ($p < 0.0001$) and 6 mg ($p < 0.0001$) but not the 1 mg dose compared with placebo. The WASO, TST, and SE (final third-of-the-night) were significantly decreased with all 3 doses of DXP compared with placebo.

Elderly with Primary Insomnia: (≥65 years of age)

Krystal et al.[7] (2010) evaluated the long-term efficacy and safety of DXP 1 mg and 3 mg in elderly subjects (mean age 71.4) with chronic primary insomnia. The study was a randomized, double-blind, parallel-group, placebo-controlled trial of 240 subjects for a period of 12 weeks. The primary endpoint was WASO on N1. The WASO decreased with DXP 1 mg compared to placebo for Nights 1, 29 and 85 by

-17.1 (p=0.02); -8.2 (p=0.30); and -12.2 (p=0.11); minutes, respectively. Patients taking DXP 3mg resulted in a decrease in WASO of -34.4 (p< 0.0001); -20.3 (p= 0.0007); -33.5 (p=0.0001) for Nights 1, 29, and 85, respectively. (Refer to Appendix A-Table 2 for further details.)

Lankford et al.[8] evaluated the efficacy and safety of DXP 6 mg in a 4 week randomized, double-blind, placebo controlled outpatient trial in 254 elderly patients (mean age 72). The primary endpoint was sTST at week 1. The mean sTST at week 1 significantly decreased -18.5 minutes (p<0.01) and -10 minutes (p<0.01) at week 4 with DXP 6 mg compared to placebo. The mean sWASO decreased -18.3 minutes (p<0.0001) at week 1 and -12.4 minutes (p <0.01) at week 4 with DXP 6 mg compared to placebo. DXP 6 mg compared to placebo improved sleep quality scores significantly at week 1 (p <0.0001) and week 4 (p <0.05). Other outcome measures including several items on the Clinician Global Impression Scale were significant at week 1 but not week 4 with DXP 6 mg compared to placebo. Compared to placebo, the Insomnia Severity Index significantly improved for DXP 6mg at week 1 (p<0.0001) and week 4 (p<0.01).

Adverse Effects:

Chronic Insomnia: Adults

The incidences of any adverse effects were 27%, 35% and 32% with placebo, DXP 3 mg and DXP 6 mg, respectively. Common adverse effect was headache, which had an incidence of 10%, 5% and 0% with placebo, DCP 3mg and DXP 6 mg, respectively. Incidence of somnolence/sedation occurred in 5%, 9% and 8% with placebo, DCP 3mg and DXP 6 mg, respectively.[5] Safety profiles of DXP 1 mg, 3 mg, and 6 mg were comparable to that of placebo with two nights of treatment.[6] No significant next-day residual effects, memory impairment complex sleep behaviors, anticholinergic effects were reported in either of the studies. Rebound insomnia (defined as the change in WASO from baseline to N36 and N37, and also percentage of patients with ≥ 35 min increase in WASO compared to baseline) was experienced by 1% in the placebo group, and 1% with DXP 3 mg.[5] Roth et al.[6] reported no statistically significant differences between placebo and any doses of DXP (1 mg, 3 mg, 6 mg) on any of the measures assessing either psychomotor function or next day alertness.

Elderly with Primary Insomnia: (≥65 years of age)

No significant differences in the incidence of any adverse effects between placebo (52%), DXP 1 mg (40%), and DXP 3 mg (38%) were demonstrated in the Krystal et al.[7] study. Common adverse effect was headache with an incidence of 14%, 3%, and 6% for placebo, DXP 1 mg, and DXP 3 mg, respectively. The incidence of somnolence occurred in 5%, 5% and 2% for placebo, DXP 1 mg, and DXP 3 mg, respectively. Incidence of adverse effects reported by Lankford et al.[8] were 27% and 31% for placebo and DXP 6mg, respectively. Common adverse effects reported by at least 2% of the patients in DXP 6mg group were somnolence/sedation (9%), dizziness (2%), dry mouth (2%) and upper respiratory tract infection (2%).[8]

Systematic Review:

Yeung et al.[3] (2014) evaluated the efficacy and adverse effects of DXP as a hypnotic. Six of nine randomized controlled trials identified included in the review compared DXP < 10mg to placebo. A meta-analysis was not able to be performed due to the differences in the study design and subjects' diagnosis. The mean differences observed with low-dose DXP versus placebo on sleep maintenance outcomes can be found in Appendix A, Table 3. The authors concluded that low-dose DXP had a small to medium effect size against placebo for sleep maintenance and sleep duration but not for sleep initiation at both immediate and short-term post-treatment in young and older adults. Low dose DXP appeared to be safe and effective in improving sleep especially for 1-2 nights. No significant differences between placebo and DXP for next-day residual effects in digit symbol substitution test (DSST), symbol copying test (SCT) and visual analog scale (VAS) for sleepiness were reported for those studies that included those measurements.[5-8,10] The risks and benefits of DXP as short-term treatment of insomnia are unclear due to the small number of studies as well as in comorbid disease states.

Drug Interactions:[1-2]

- Central Nervous System (CNS) depressants: When taken with DXP, the sedative effects of other CNS depressants such as benzodiazepines, opioids, tricyclic antidepressants, and alcohol could potentially be potentiated.

- Sertraline could potential increase the AUC and Cmax of DXP. Psychomotor function could potentially decrease more with the combination.
- Cimetidine increased the Cmax and AUC when co-administered with DXP. The maximum dose of DXP should be 3 mg when co-administered with cimetidine.

Monitoring:
There are no specific laboratory tests recommended.

Dosage and Administration[1]
Recommended Initial Dose:
Adults: 6mg, once daily (3mg once daily dose may be appropriate for some patients, if clinically indicated)
Elderly (≥ 65 years old): 3mg, once daily. (The daily dose can be increased to 6mg, if clinically indicated)

For a faster onset, tablets should not be taken within 3 hours of a meal to minimize the potential for next day effects.

Summary:
Low dose doxepin (3 mg and 6 mg) is FDA approved for the treatment of sleep maintenance. It has no known activity at benzodiazepine recognition sites or at other sites on the gamma-aminobutyric acid (GABA) receptor complex. Low dose doxepin is effective in reducing objective and subjective parameters of sleep maintenance endpoints. Trials have been conducted in young and older adults with the longest trial (12 weeks) conducted in the elderly (mean age of 71 years) evaluating the dose of doxepin 3 mg. During clinical trials, no overall differences in safety were observed in elderly compared to the young – middle aged adults. Headache and somnolence were the most common side effects associated with low dose doxepin. No significant next-day residual effects, memory impairment, complex sleep behaviors, or anticholinergic effects with low-dose doxepin were reported. Rebound insomnia studied in one trial was experienced by 1% in placebo group, 1% in doxepin 3 mg group, and 4% in doxepin 6 mg group. Limited data is available on the efficacy and safety long-term, use of 6 mg in the elderly after one month, and the use in patients with comorbid conditions.

Introduction
The purposes of this abbreviated review are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating doxepin (3 mg, 6 mg) tablets for possible addition to the VA National Formulary; and (2) define its role in therapy.

Pharmacology/Mechanism of Action[1,2]
Doxepin is a tricyclic antidepressant. At low doses it is a potent H_1 antagonist. It has some affinity for the 5-HT_{2a} receptor which may contribute to its effect on sleep maintenance. Histamine has a role in the regulation of sleep-wakefulness and H_1 receptors are the primary histaminergic mediator of arousal and the sleep-wake cycle. When histamine is released, it increases wakefulness and prevents sleep. Because histamine release may be relatively higher towards the end of the night, more histamine is blocked with H_1 antagonism, thus promoting maintenance of sleep into the 7^{th} and 8^{th} hours of the night, with the absence of meaningful evidence of next day residual effects. Low dose doxepin does not have any activity at benzodiazepine recognition sites or at other sites on the gamma-aminobutyric (GABA) receptor complex as do other currently approved medications for the treatment of insomnia.

FDA Approved Indication[1,2]
Doxepin tablet was approved by the FDA on March 17, 2010 and is indicated for the treatment of insomnia characterized by difficulties with sleep maintenance.

Potential Off-label Uses
This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Doxepin has been used for certain chronic and neuropathic pain; anxiety; burning mouth syndrome. Low-dose doxepin tablets have been used in combination with sertraline to treat severe agitated-anxious depression with significant GI complaints (case reports).

Current VA National Formulary Alternatives

Temazepam is FDA approved for the treatment of short-term insomnia. It is an intermediate acting benzodiazepine and could potentially be used to treat insomnia characterized by difficulties with sleep maintenance.

Dosage and Administration[1-2]

Recommended Initial Dose:
Adults: 6mg, once daily (*3mg once daily dose may be appropriate for some patients, if clinically indicated)*
Elderly (≥ 65 years old): 3mg, once daily. *(The daily dose can be increased to 6mg, if clinically indicated)*

For a faster onset, tablets should not be taken within 3 hours of a meal to minimize the potential for next day effects.

Pharmacokinetics/Pharmacodynamics[1-4]

Distribution: Doxepin is approximately 80% bound to plasma proteins.
Metabolism: Doxepin is extensively metabolized by oxidation and demethylation. The primary metabolite is N-desmethyldoxepin (nordoxepin). The primary metabolite undergoes further biotransformation to glucuronide conjugates. See Table 1 for further pharmacokinetic parameters.

Table 1: Doxepin and Nordoxepin Pharmacokinetic Parameters[+]

Parameters	Doxepin (Nordoxepin)
Elimination half-life (h)	15.32 (31.3 hours)
T_{max} (h)	3.5 (2.0-6.0)
C_{max} (ng/mL)	0.8864 (59.4)
$AUC_{0-\infty}$ (ng*h/mL)	15.19 (69.1)
Metabolism	Doxepin is metabolized primarily by P450 CYP2C19 and CYP2D6 (major); CYP1A2 and CYP2C (lesser extent). Doxepin is not a P-gp substrate.
Food Effect	The AUC Increased 41% and Cmax by 15% with a high fat meal compared to the fasted state. Under fed conditions, the time to reach maximum plasma concentration (median-Tmax) was delayed by 3 hours. Mean half-life (t1/2) was similar under fed and fasted conditions
Elimination	Doxepin is excreted in the urine mainly in the form of glucuronide conjugates. Less than 3% of a doxepin dose is excreted in the urine as parent compound or nordoxepin.

[+] Median time based on single-center Phase 1, randomized, open-label, single 6mg dose, two-way crossover study involving 16 healthy adults, aged 18-45, 10 females and 6 males.

Table 2: Special Populations and Considerations for Doxepin Low Dose[1-2]

Doxepin Low Dose (3 mg, 6 mg)	
Dose in Elderly	The recommended starting dose 3 mg once daily.
Dose in Hepatic Impairment	The effects of doxepin in patients with hepatic impairment have not been studied. Because doxepin is extensively metabolized by hepatic enzymes, patients with hepatic impairment may display higher doxepin concentration than healthy individuals.
Dose in Renal Impairment	No dosage adjustment is expected because small amounts of doxepin and nordoxepin are eliminated in the urine.
Poor Metabolizer of CYPs	Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.
Pregnancy Category	C; Administration to nursing mothers is not recommended.
Pediatrics (< 18 years of age)	The safety and effectiveness have not been evaluated

Efficacy

Primary Measures of sleep maintenance include: Wake After Sleep Onset (WASO), subjective WASO (sWASO), Total Sleep Time (TST), subjective TST (sTST), and Sleep Efficiency (SE), overall. Waking up

too early or inability to sleep through to desire sleep period is measured in clinical studies as SE in Hour 8 and/or SE in the Last Quarter of the Night.

Adults: Objective Measurements

Krystal et al.[5] (2011) conducted a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of DXP 3 mg (n=75) and 6 mg (n= 73) compared to placebo (n=73) in patients with primary insomnia (per DMS-IV-TR criteria) using polysomnography (PSG). The patients were treated for 35 consecutive nights followed by 2 nights of single-blind placebo to evaluate discontinuation effects (rebound and withdrawal symptoms). The primary endpoint was WASO on Night 1 (N1). Compared with placebo, DXP 3 and 6 mg significantly improved objective WASO on N1, 15 and 29 (see Appendix A). Mean WASO significantly decreased with DXP 3 mg by 26 minutes ($p \leq 0.0001$) and 6 mg by 30.5 minutes ($p \leq 0.0001$), compared to placebo on N1. Total sleep was statistically improved with DXP 3 for N1 ($p \leq 0.0001$), N29 ($p < 0.05$) while DXP 6 mg improved that measurement for N1 ($p \leq 0.0001$), N15 ($p < 0.01$) and N29 ($p \leq 0.0001$). In terms of early morning awakenings, DXP 3 demonstrated significant improvements in sleep efficiency in the final quarter of the nights on N1 ($p<0.01$), N15 ($p<0.05$), while DXP 6 mg resulted in significant improvements for N1 ($p \leq 0.0001$) and N15 ($p < 0.05$) and N29 ($p < 0.01$). Rates of discontinuation were low, and the safety profiles were comparable across the three treatment groups. No significant next-day residual effects, memory impairment, complex sleep behaviors, anticholinergic effects, weight gain, or increased appetite were reported. No evidence of significant withdrawal or rebound insomnia (defined as the change in WASO from baseline to N36 and N37, and also percentage of patients with ≥ 35 min increase in WASO compared to baseline) was evident after DXP discontinuation. Refer to Appendix A-Table 1 for more details.

Roth et al.[6] (2007) randomized 67 adults (18-64 years) with chronic primary insomnia to 1 mg, 3 mg, and 6 mg DXP and placebo in a double-blind four-period crossover study consisting of 2 polysomnographic (PSG) assessment nights as well as patient-reported measures. Wake Time During Sleep (WTDS) was the primary endpoint. Treatment periods were 2 nights of study drug followed by 8 hours of PSG recording in a sleep laboratory followed by a 5 or 12-day drug-free interval. Psychomotor assessments (Digit-Symbol Substitution Test (DSST), Symbol-Copying Task (SCT), and a visual analogue scale (VAS) for sleepiness) were conducted prior to each treatment period. Subjective questionnaires were completed 9 hours post drug administration for psychomotor function. The WTDS significantly was reduced with DXP 3 mg ($p < 0.0001$) and 6 mg ($p < 0.0001$) but not the 1 mg dose compared with placebo. The WASO, TST, and SE (final third-of-the-night) were significantly decreased with all 3 doses of DXP compared with placebo. The sWASO did not significantly decrease with any of the three doses of DXP compared with placebo. The sTST significantly increased with DXP 6mg ($p=0.0190$) dose but not with the 1 mg or 3 mg doses compared with placebo. No statistically significant differences between placebo and any doses of DXP on any of the measures assessing either psychomotor function or next day alertness were observed.

Transient Insomnia:

Roth et al.[7] (2010) studied 565 healthy adults (22-55 years of age) with induced transient insomnia in a randomized double-blind, placebo-controlled single dose study of DXP 6 mg compared to placebo. Latency to persistency sleep (LPS), the primary endpoint, was significantly lower for DXP 6 mg compared with placebo ($p<0.0001$). Significant improvement were also seen in sleep maintenance (WASO, sWASO, TST, sTST), and early morning awakenings (SE at hours 7 and 8) with DXP 6 mg compared to placebo.

Elderly: Subjective Measurements [8,9]

Krystal et al.[8] (2010) evaluated the long-term efficacy and safety of DXP 1 mg and 3 mg in elderly subjects (mean age 71.4) with chronic primary insomnia. The study was a randomized, double-blind, parallel-group, placebo-controlled trial of 240 subjects for a period of 12 weeks. The primary endpoint was WASO on N1. The WASO decreased with DXP 1 mg compared to placebo on N1,N 29 and N85 by -17.1 ($p =0.02$); -8.2 ($p =0.30$); and -12.2 ($p =0.11$); minutes, respectively. Patients taking DXP 3mg resulted in a decrease in WASO of -34.4 ($p < 0.0001$); -20.3 ($p = 0.0007$); -33.5 ($p =0.0001$) on N1, N29, and N85, respectively. Other objective sleep maintenance measures (TST, SE last quarter) significantly improved with DXP 3 mg on N1, N29 and N85. Patient-reported significant improvement in sTST at Weeks 1 ($p=0.0043$); 4 ($p= 0.00350$); and 12 ($p=0.0001$) for DXP 3 mg and at Weeks 4 ($p =0.0343$) and 12 ($p=0.0027$) for DXP 1mg.[3] Clinical Global Impression scale which assessed the severity and improvement of insomnia completed by the patient's clinician, significantly improved with DXP 3mg for Weeks 1 (p

<0.01), 4 (p <0.05), 12 (p <0.001) compared to placebo. Patients' perspective on their insomnia condition significantly improved with DXP 3mg for Weeks 1, (p<0.05); 4 (p<0.01), 12 (p<0.01) compared to placebo. (Refer to Appendix A-Table 2 for further details.)

Lankford et al.[9] conducted a randomized, double-blind, placebo controlled multicenter trial to determine the efficacy and safety of DXP 6 mg in a four-week outpatient trial in 254 elderly adults ≥65 years of age (mean age 72) with primary insomnia (defined by DSM-IV-TR). The primary endpoint was sTST at Week 1. Other subjective outcomes measured included sWASO, sLSO, sleep quality, and a Patient Global Impression scale (PGI). Patients eligible for randomization had to meet the Interactive Voice Response System (IVRS) criteria: ≥ 80 min of subjective wake sWASO, ≥ 30 min of LSO, ≤ 6.5 hours sTST for at least 4 nights during the one week single-blind placebo lead-in period, and also have a ≤ 2 hour variation in bedtime. Of the 525 patients screened, 255 patients were randomized. A total of 237 subjects (93%) completed the study. The two treatment groups did not differ significantly on the sleep onset endpoint at any time point. Sleep quality was significantly improved at Weeks 1, 3 and 4 for DXP 6mg versus placebo (PBO). Improvements in all IVRS sleep data were sustained across the four-week trial. Subjective TST was significantly improved relative to placebo at Weeks 1-4 for DXP 6 mg suggesting no evidence of tolerance to the sleep duration effects. Additionally, sWASO was significantly improved relative to placebo at all four weekly assessments for DXP 6 mg. Sleep onset, (LSO) was not improved at any time point The Insomnia Severity Index was significantly improved relative to placebo for DXP 6mg at all four weeks. Treatment with DXP 6mg resulted in significant improvements in the CGI-Severity and CGI-Improvement scale scores relative to placebo at Weeks 1 and 2. The PGI resulted in significant improvements for four of the five items at each visit with DXP 6 mg compared to placebo. These items included: "helped sleep," "shortened onset," "increased duration", and "drug strength just right". The item "got better sleep" improved but was not significantly changed with DXP compared to placebo (Refer to Table 3 for more details).

Table 3: Subjective Efficacy Endpoints with 6mg Doxepin in the Elderly[9]

	Placebo (SD) n= 125	DXP 6mg (SD) n=130
Primary Endpoint (week 1 only)		
Baseline Mean sTST (min)	293.5 (49.1)	283.1 (50.0)
Mean sTST (min) at Week 1	316.7 (56.2)	335.2** (61.2)
Week 4	336.4 (64.7)	346.1** (66.4)
Secondary Endpoints		
Baseline sWASO (min)	112.0 (46.6)	116.5 (49.1)
sWASO at week 1	97.4 (50.2)	79.1***(49.0)
sWASO at week 4	78.9 (56.5)	66.5 **(43.9)
Sleep Quality		
Baseline	-0.7 (1.0)	-0.7 (0.9)
Week1	-0.3 (1.0)	0.2*** (1.0)
Week 4	0.2 (1.1)	-0.4* (1.0)
CGI-Severity scale		
Baseline	4.8 (0.6)	4.7 (0.8)
Week 1	4.9 (0.9)	4.0* (1.1)
Week 4	3.9 (1.2)	3.7 (1.1)
CGI-Improvement		
Baseline	N/A	N/A
Week 1	3.4 (0.9)	3.0** (1.1)
Week 4	3.1 (1.1)	2.8 (1.1)
Insomnia Severity Index		
Baseline	17.5 (4.5)	17.9 (4.3)
Week 1	15.8 (4.6)	14.0*** (4.9)
Week 4	14.0 (5.9)	(12.5** (5.5)

PBO=Placebo; DXP=Doxepin; Sleep Quality (scale from -3 to 3, -3 = extremely poor, -2 = very poor, -1 = poor, 0 = fair, 1 = good, 2=very good, 3= excellent); CGI= Clinical Global Scale (assessed the severity of insomnia and the therapeutic effect of the study drug and is completed by the patient's clinician), Patient Global Impression scale included 5 questions pertaining to the therapeutic effect of the study drug, Insomnia Severity Index consisted of 7 questions related to patients' self-assessment of the severity of their insomnias. SD= Standard deviation, DXP= doxepin; SWASO= Subjective wake after sleep onset, sTST= subjective total sleep time; *p= 0.05 versus placebo; ** = p< 0.01; ***p=0.0001.

Scharf et al.[10] conducted a 2-night study similar to Roth et al.[6] with 76 elderly patients (mean age 71 years) comparing DXP 1 mg, 3 mg, and 6 mg and placebo. The primary efficacy endpoint was WTDS. All 3 DXP doses produced significant improvement in WTDS versus placebo.

Adverse Effects:

Chronic Insomnia: Adults

The incidences of any adverse effects were 27%, 35% and 32% in placebo, DXP 3 mg and DXP 6 mg, respectively. Common adverse effect was headache, which had an incidence of 10%, 5% and 0% in placebo, DXP 3mg and DXP 6 mg, respectively. Incidence of somnolence/sedation occurred in 5%, 9% and 8% in placebo, DXP 3mg and DXP 6 mg, respectively.[5] Safety profiles of DXP 1 mg, 3 mg, and 6 mg were comparable to that of placebo with two nights of treatment.[6] No significant next-day residual effects, memory impairment complex sleep behaviors, anticholinergic effects were reported in either of the studies. Rebound insomnia (defined as the change in WASO from baseline to N36 and N37, and also percentage of patients with ≥ 35 min increase in WASO compared to baseline) was experienced by 1% in the placebo group, and 1% in doxepin 3 mg.[5] Roth et al.[6] reported no statistically significant differences between placebo and any doses of DXP (1 mg, 3 mg, 6 mg) on any of the measures assessing either psychomotor function or next day alertness. (Refer to Appendix A-Table 2 for further details.)

Elderly with Primary Insomnia: (≥65 years of age)

No significant differences in the incidence of any adverse effects between placebo (52%), DXP 1 mg (40%), and DXP 3 mg (38%) was demonstrated by Krystal et al.[8] Common adverse effect was headache with an incidence of 14%, 3%, and 6% for placebo, DXP 1 mg, and DXP 3 mg, respectively. The incidence of somnolence occurred in 5%, 5% and 2% for placebo, DXP 1 mg, and DXP 3 mg, respectively. Incidence of adverse effects reported by Lankford et al.[8] was 27% and 31% for placebo and DXP 6mg, respectively. Treatment emergent adverse events (TEAEs) were similar between placebo and DXP 6mg group. The most frequently reported adverse effects reported by at least 2% of patients in the DXP 6mg group were somnolence/sedation (9%), dizziness (2%), dry mouth (2%) and upper respiratory tract infection (2%). Rates of discontinuation were lower in the DXP 6 mg group compared with placebo, 5% vs. 10%, respectively. No reports of complex sleep behavior, cognitive disorder, memory impairment, and anticholinergic effects, changes in neurological assessments or electrocardiogram, or weight gain were reported with DXP across the four weeks of treatment.[8]

Cardiac Safety:[11]

In a double blind, randomized, placebo-controlled, parallel group study in 206 healthy adult subjects (aged 18-45), cardiac repolarization was assessed with serial ECG recordings at baseline and on day 7 of treatment for up to 23.5 hours after dosing with DXP 6mg and 50 mg. The primary outcome was the time-matched change from baseline in individually correct QT (QTcL) intervals. Neither doses of DXP increased the QTc interval, the QRS duration, or the PR interval suggesting no effect on cardiac repolarization.

Contraindications[1,2]

- Known hypersensitivity to doxepin, or any of its active ingredients, or other dibenzoxepines.
- Individuals currently on monoamine-oxidase inhibitors (MAOIs) or who have used MAOIs within the past 2 weeks.
- Individuals with untreated narrow-angle glaucoma or severe urinary retention.

Warnings and Precautions[1]

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient.

Patients should be cautioned about potential additive effects of DXP used in combination with CNS depressants or sedating antihistamines. Patients should not consume alcohol with doxepin. Doxepin should be discontinued for patients who report a “sleep-driving” episode or other complex behavior episode.

The potential for self-harm (e.g., intentional overdose) is high in patients with depression and thus, the least amount of drug should be available to them at any one time especially if signs and symptoms of depression, including suicidal thoughts and actions has been reported with the use of hypnotics.

Special Populations for Adult Population[1-2]

Pregnancy: Pregnancy category C; given the lack adequate and well-controlled studies in pregnant women, the use of doxepin should be considered in this population only if the benefits outweigh the risks

Nursing Mothers: Doxepin is excreted in human milk. There is a report of apnea and drowsiness occurring in a nursing infant whose mother was taking higher dose of DXP to treat depression. The administration of DXP to nursing mothers is not recommended.

Geriatric Use: No overall differences in safety or effectiveness were observed between geriatrics and younger adult subjects, however a greater sensitivity of some older individuals cannot be ruled out as sleep-promoting drugs may cause confusion and over-sedation in elder. It is recommended to initiate DXP at 3 mg dose in these patients.

Renal Impairment: The effects of renal impairment on the pharmacokinetics of DXP have not been studied. Because only small amounts of doxepin and nordoxepin are eliminated in the urine, renal impairment would not be expected to result in significant altered doxepin concentrations.

Hepatic Impairment:

The effects of hepatic impairment of the pharmacokinetics of DXP low doses have not been studied. Because DXP is extensively metabolized by hepatic enzymes, patients with hepatic impairment may display higher doxepin concentrations than healthy individuals.

Sleep Apena:

Doxepin has not been studied in patients with obstructive sleep apnea. Since hypnotics have the capacity to depress respiratory drive, precautions should be taken if DXP is prescribed to patients with compromised respiratory function. In patients with severe sleep apnea, doxepin is not recommended for use.

Drug Interactions[1]

Doxepin is primarily metabolized by hepatic cytochrome P450 isoezymes CYP2C19 and CYP2D6, and to a lesser extent, by CYP1A2 and CYP2C. Inhibitors of these isoezymes may increase the exposure of doxepin. Doxepin is not an inhibitor of any CYP isoezymes at therapeutically relevant concentrations. The ability to induce CYP isoezymes is not known. Since DXP is metabolized by CYP2C19 and CYP2D6, inhibitors of these CYP isoezymes may increase the exposure of doxepin.

Doxepin may potentiate the sedative effects of alcoholic beverages, sedating antihistamines and other CNS depressants.

MAOI-See Contraindication

Cimetidine: When cimetidine 300mg BIS was co-administered with a single dose of doxepin 6mg, there was approximately a 2-fold increase in doxepin Cmax and AUC, compared to doxepin given alone. A maximum dose of doxepin in adults and elderly should be 3 mg, when doxepin is co-administered with cimetidine.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-

Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	First Databank	ISMP	Clinical Judgment
Doxepin 3mg, 6mg tab	Digoxin Doxapram Doxazosin Doxidan Doxycycline	None	None	Doxylamine (OTC)
Silenor	None	None	None	Simcor Sinequan Silodosin Silexin (OTC)

Acquisition Costs

Refer to VA pricing sources for updated information.

Conclusions

Low dose doxepin (3 mg and 6 mg) is FDA approved for the treatment of sleep maintenance. It has no known activity at benzodiazepine recognition sites or at other sites on the gamma-aminobutyric acid (GABA) receptor complex. Low dose doxepin is effective in reducing objective and subjective parameters of sleep maintenance endpoints. Trials have been conducted in young and older adults with the longest trial (12 weeks) conducted in the elderly (mean age of 71 years) with doxepin 3 mg dose. During clinical trials, no overall differences in safety were observed in elderly compared to the young –middle aged adults. Headache and somnolence were the most common side effects associated with low dose doxepin. No significant next-day residual effects, memory impairment, complex sleep behaviors, or anticholinergic effects with low-dose doxepin were reported. Rebound insomnia studied in one trial was experienced by 1% in placebo group, 1% in doxepin 3 mg group, and 4% in doxepin 6 mg group. Limited data is available on the efficacy and safety long-term, use of 6 mg in the elderly after one month, and the use in patients with comorbid conditions.

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Appendix A: Clinical Trials

Table 1: Efficacy and Safety of Doxepin 3 and 6 mg in a 35-day Sleep Laboratory Trial in Adults with Chronic Primary Insomnia

<table>
<tr><th>Trial/ Objective/ Funding</th><th>Study Design</th><th>Results and Conclusions</th></tr>
<tr>
<td>Krystal et al. (2011)

Objective: To study the efficacy and safety of doxepin 3 and 6 mg in a 35 day sleep laboratory Trial in Adults with Chronic Primary Insomnia

This study was funded by Somaxon Pharmaceuticals.</td>
<td>Design: R, DB, PC, parallel group, MC (22 sleep centers in US)
Initial Screening Phase: medical, sleep, and psychiatric history, PE, VS measurements, clinical laboratory tests, and ECG

If eligible, record sleep pattern in diary: ≥7 days sleep assessment

If eligible then, 2 weeks of single-blind placebo dosing. First 2 nights in sleep lab.

2 nights PSG Screening Phase:
Criteria: LPS > 10 min; mean WTDS (wake time during sleep) ≥60 min, with no night < 45 min; and TST > 240 and ≤ 400 min on both screening nights. If eligible, then single-blind placebo x 5 consecutive nights at home. After DB therapy was initiated, 2 nights of 8-h PSG recording were done N1/N2; N15; N16; and N29 and N30). During the discontinuation period (N36 and N37), patients received single-blind placebo and 2 final nights of 8-h PSG recording.

Inclusion:
• 18-64 years with DSM-IV-TR diagnosis of primary insomnia who reported sleep maintenance difficulty for ≥3 months

Exclusion:
• Excessive use of alcohol, nicotine, or caffeinated beverages
• Intentional napping more than twice per week
• Variation in bedtime > 2 h on 5 of 7 nights
• Use of a hypnotic or any other medication known to affect sleep.
• ≥ 10 apnea/hypopnea events or periodic leg movements with arousals/h of sleep on PSG screening.
Treatment x 35 days: (administered 30 minutes before</td>
<td>Participants: 1082 patients screened. 229 patients were randomized (Mean age 44.5 years, age range: 18-64); Mean BMI 27.3; 73% female, 27% male, 48% Caucasian, 33% African American, 16% Hispanic,3% other.
203 (89%) completed study. 26 (11%) discontinued the study, 8 (3.5%) discontinued after randomization, but before receiving the study drug (not included in ITT or safety analyses); 18 patients (11%) discontinued during the double-blind period. Early discontinuation rates and baseline characteristics were comparable across treatment groups..
Efficacy: PSG Measures
<table>
<tr><th colspan="2">Objective Sleep Parameters</th><th>Placebo (SD)
n=76</th><th>Doxepin 3mg (SD)
n=77</th><th>Doxepin 6mg (SD)
n=76</th></tr>
<tr><td rowspan="4">Mean WASO (min) [Sleep Maintenance]</td><td>Baseline</td><td>65.7 (36.8)</td><td>67.8 (33.6)</td><td>65 (33.2)</td></tr>
<tr><td>N1 (1° Endpoint)</td><td>66.8 (49.9)</td><td>41.4*** (31.5)</td><td>36.3*** (26.1)</td></tr>
<tr><td>N15</td><td>60.5 (51.9)</td><td>44.7**(29.2)</td><td>41.7** (29.4)</td></tr>
<tr><td>N29</td><td>60.5 (38.8)</td><td>47.2* (43.5)</td><td>40.7**(37.3)</td></tr>
<tr><td rowspan="4">TST (min)</td><td>Baseline</td><td>380.2 (44.4)</td><td>380.3 (46.1)</td><td>380.3 (43.1)</td></tr>
<tr><td>N1</td><td>373.9 (71.7)</td><td>415.3*** (41.7)</td><td>420.5*** (37.1)</td></tr>
<tr><td>N15</td><td>389.2 (62.8)</td><td>402.1 (50.4)</td><td>411.4** (50.4)</td></tr>
<tr><td>N29</td><td>391.5 (48.9)</td><td>408.0* (53.5)</td><td>419.5*** (44.2)</td></tr>
<tr><td rowspan="4">SE in the last quarter (early morning awakenings)</td><td>Baseline</td><td>78.3 (14.6)</td><td>79.1 (15.5)</td><td>79.8 (15.0)</td></tr>
<tr><td>N1</td><td>79.9 (20.4)</td><td>88.3** (13.8)</td><td>89.8*** (9.4)</td></tr>
<tr><td>N15</td><td>81.2 (19.1)</td><td>86.6* (13.6)</td><td>87.4* (12.5)</td></tr>
<tr><td>N29</td><td>80.7 (16.7)</td><td>85.1 (14.1)</td><td>87.8** (14.0)</td></tr>
<tr><td rowspan="4">LPS (min)
[Sleep onset]</td><td>Baseline</td><td>37.9 (28.4)</td><td>35.9 (29.8)</td><td>39.1 (34.1)</td></tr>
<tr><td>N1</td><td>44.8 (54.6)</td><td>26.7** (23.4)</td><td>27.1** (25.4)</td></tr>
<tr><td>N15</td><td>34.0 (39.0)</td><td>38.0 (39.6)</td><td>31.7 (35.9)</td></tr>
<tr><td>N29</td><td>32.0 (35.3)</td><td>28.5 (26.0)</td><td>24.6 (21.1)</td></tr>
</table>
N=night; *P < 0.05 vs. placebo; **P < 0.01; ***P ≤ 0.0001.</td>
</tr>
</table>

bedtime)
DXP 3 mg; 6 mg or placebo

Study period included 2 nights of 8h PSG recordings with questionnaire assessing sleep characteristics for next day residual effects.

Assessment
Objective Primary Endpoint: WASO on Night 1
Other Objective Endpoints:

- WASO at other time points
- LPSL Latency Persistent Sleep
- NAASO (number of awakenings after sleep onset)
- TST: Total Sleep Time
- SE-quarter of the night and by hour
- WTAS: wake time after sleep from the last epoch of sleep until the end of the 8-h recording period
- Sleep architecture: percentages and duration (in min) of stage 1, 2, and 3/4 sleep, REM sleep, and latency to REM sleep

Subjective: Morning questionnaire including measures of latency to sleep onset (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) for Nights, 1, 15, and 29.

Next-day Residual Effects:
Objective: Digit Symbol Substitution Test (DSST) and Symbol Copying Test (SCT) and
Subjective:100 mm visual analog scale (VAS)
Safety: laboratory test (hematology, serum chemistry, UA), VS,12-lead ECG and PE

Rebound Insomnia: change in WASO from baseline to N36 and N37 and defined as the percentage of patients with ≥ 35-min increase in WASO compared to baseline.

Withdrawal: Assessed during the discontinuation period using the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ), vital signs, and spontaneously reported adverse effects. Withdrawal was defined as the emergence of ≥ 3 new symptoms or the worsening of previous symptoms during the discontinuation period on the BWSQ.

Subjective Results:

Subjective Sleep Parameters		Doxepin 3mg (p) n=77	Doxepin 6mg (p) n=76
Mean sWASO (min) [Sleep Maintenance]	N1	-10.2* (0.0003)	-14.2* (0.0004)
sTST (min)	N1	11.0* (0.0088)	17.3* (0.0135)
SE in the last quarter (early morning awakenings) [Sleep quality]	N1	(0.0068)	(<0.0001)
sLSO (min)	N1	NS	(0.0492)

sWASO= subjective Wake After Sleep Onset; LSO= Latency to Sleep Onset , NS= Not significant.* analysis done via mixed-effect model repeated measures (MMRM) approach compared to placebo.

Tolerance to Sedative Effect: No evidence to sleep maintenance per WASO, TST, SE measurements. LPS results are suggestive of the development of tolerance for sleep onset effects.

Safety:
Sleep architecture: DXP 3 and 6 mg increased the duration of stage 2. (data not shown)
Adverse Events: 20 (27%) placebo; 26 (*35%) DXP 3mg; 23 (32%) in DXP 6mg.The most common AEs reported headache, somnolence/sedation, and nausea.
Discontinuation Rates: 26 (11%): 12% placebo; 12% DXP 3 mg 11% DXP 6 mg. Withdrawal due to AEs: 1%, 3%, 4% in placebo, DXP 3 mg and DXP 6 mg, respectively.
Rebound Insomnia: Based on PSG defined criteria, 1% placebo, 1% DXP 3 mg, and 4% of DXP 6 mg group experienced rebound insomnia.
Withdrawal effects: 8% of patient in each of the 3 groups experienced adverse events during the discontinuation period. No evidence of physical dependence, withdrawal syndrome, or worsening insomnia. Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) data: no evidence of withdrawal syndrome. Two patients experienced predetermined BWSQ withdrawal criteria (1 in placebo group, 1 in DXP 3 mg) per BWSQ
Next-day Residual Sedation: No significant differences between placebo and any dose of DXP on any measures accessing either psychomotor function (DSST and SCT; or next day alertness (VAS) at any time point.

Conclusions:

- Both DXP 3 mg and 6 mg doses improved WASO on N1 (primary endpoint); $p \leq 0.0001$ compared to placebo with no evidence of tolerance to the sleep maintenance effects. However, the number of minutes in the DXP 6 mg group slightly decreased from N 15 to N 29. Improvement in WASO on N1 for DXP 3 mg and 6 mg compared with placebo groups did not differ across the ethnic subgroups.
- TST significantly improved on N1 ($p<0.0001$) and N29 ($p=0.0262$) with DXP 3mg compared to placebo. DXP 6mg significantly improved TST on N1 ($p<0.0001$), N15 ($p=0.0262$) and N29 ($p=0.0003$) compared to placebo.
- SE in the last quarter of the night improved on N1 ($p=0.0008$) and N15 ($p=0.0220$) for DXP 3mg, and on N1 ($p<0.0001$), N15 ($p=0.022=39$), and N29 ($p=0.0029$) for DXP 6mg compared to placebo. Statistical

		differences were seen during the same respective time periods with both doses for SE in Hour 8. • DXP 3 mg and 6 mg were superior to placebo on sWASO on N1 only. However, the double-blind average across N1, N15, and N29 was significant with both doses compared to placebo. • Similar rebound insomnia (based on WASO criteria) was experienced by all groups. • No dose-related effects on safety and a comparable overall rate of AEs and study discontinuations with DXP and placebo. • No significant next-day residual effects per DSST, SCT and VAS ratings. • Significant early morning awakenings reduction as measured by sleep efficiency % in the last quarter of the night with DXP 3mg on N 15 and DXP 6mg on N15 and N29. **Quality Assessment:** (Good) although may not be generalized to VA population Study Critique: • Strength: R, DB study; primary endpoint achieved statistical significance; objective and subjective sleep parameters evaluated. • Weakness: Tolerance and withdrawal cannot be entirely ruled out with longer duration. • Limitations: Population was limited to primary insomnia patients with mean age of 45 years so results may not be applied to patients with co-morbidities or to the VA population. Preparation and publication of article was supported by Somaxon Pharmaceuticals, 4/7 authors were employees of Somaxon; three authors received financial support from company.

R = Randomized; DB = double-blind; PC = placebo-controlled; MC = multicenter; LPS= Latency to persistent sleep; PE= physical exam; VS= vital signs; PSG= polysomnography; TST = Total Sleep Time; ECG= Electrocardiogram

Table 2: Efficacy and Safety of Doxepin 1 mg and 3 mg in a 12-week Sleep Laboratory and Outpatient Trial of Elderly Subjects with Chronic Primary Insomnia

<table>
<tr><th>Trial/ Objective/Funding</th><th>Study Design</th><th>Results and Conclusions</th></tr>
<tr><td>Krystal et al. (2010)

Objective: To study the efficacy and safety of doxepin 1 and 3 mg in elderly subjects with chronic primary insomnia.

This study was funded by Somaxon Pharma-ceuticals.</td><td>Design: R, DB, PC, parallel group, MC (31 sleep centers in US)

Initial Screening Phase: medical, and psychiatric history, PE, VS measurements, clinical laboratory tests, and ECG

If eligible, record sleep history: ≥7 days sleep diary

If eligible then, 1 week of single-blind placebo initiated. First 2 nights were PSG Screening.

2 nights PSG Screening Phase:
Criteria: LPS > 10 min; mean WTDS ≥ 60 min and TST> 240 and ≤ 390 min. If eligible then single-blind placebo x 5 consecutive nights at home

Inclusion:
• ≥ 65 years with a DSM-IV-TR diagnosis of</td><td>Participants: 923 patients screened. 240 patients were randomized (Mean age 71 years, age range: (64-93); 65% female, 35% male, 80% Caucasian, 9% African American, 9% Hispanic,2% other.
214 (89%) completed study.
Efficacy: PSG Measures
<table>
<tr><th colspan="2">Objective Sleep Parameters</th><th>Placebo (SD) n=81</th><th>Doxepin 1mg (SD) n=77</th><th>Doxepin 3mg (SD) n=82</th></tr>
<tr><td rowspan="4">Mean WASO (min) [Sleep Maintenance]</td><td>Baseline</td><td>119.5 (37.7)</td><td>120.1. (35.0)</td><td>117.9 (28.2)</td></tr>
<tr><td>N1 (1° Endpoint)</td><td>108.9 (46.)</td><td>91.8** (47.1)</td><td>74.5*** (37.9)</td></tr>
<tr><td>N29</td><td>104.6 (53.5)</td><td>96.4 (45.3)</td><td>84.3*** (40.9)</td></tr>
<tr><td>N85</td><td>109.2 (50.8)</td><td>97.0* (44.2)</td><td>75.7***(37.6)</td></tr>
<tr><td rowspan="2">TST (min)</td><td>Baseline</td><td>320.6 (40.3)</td><td>322.4 (39.9)</td><td>326.9 (33.2)</td></tr>
<tr><td>N1</td><td>339.7 (54.4)</td><td>359.1* (53.1)</td><td>382.0*** (44.2)</td></tr>
</table>
</td></tr>
</table>

primary insomnia who reported sleep maintenance difficulty for ≥3 months

Exclusion:

- Excessive use of alcohol, nicotine, or caffeinated beverages
- Intentional napping more than twice per week
- Variation in bedtime > 2 h on 5 of 7 nights
- Use of a hypnotic or any other medication known to affect sleep.
- ≥ 15 apnea/hypopnea events or periodic leg movements with arousals/h of sleep on PSG screening.

Treatment x 12 weeks: (administered 30 min prior to bedtime)
DXP 3 mg; DXP 6mg; or placebo

Study period included 2 nights of 8h PSG recordings with questionnaire assessing sleep characteristics for next day residual effects.
Assessment
Objective Primary Endpoint: WASO on Night 1

Other Objective Endpoints:

- WASO at other time points
- LPS
- NAW: (Number of awakenings after sleep onset)
- TST: (Total Sleep Time)
- SE: (Sleep Efficiency)
- WTAS: wake time after sleep
- SE- (Sleep Efficiency quarter of the night and by hour of the night)

Subjective:

- Clinical Global Impression (CGI) scale: completed by patient's clinician assessing the CGI-Severity and CGI-Improvement
- Patient Global Impression (PGI) scale, completed by patient (5 questions)
- Insomnia Severity Index: completed by patient (7 questions)

	N29	345.0 (59.1)	344.4 (55.1)	363.9* (54.0)
	N85	343.7 (57.7)	360.5* (47.2)	383.7.5*** (42.2)
SE in the last quarter (early morning awakenings)	Baseline	64.7 (17.0)	64.4 (17.0)	65.0 (15.3)
	N1	62.1 (24.3)	72.5** (19.4)	76.6*** (16.7)
	N29	64.7 (24.9)	68.2 (22.5)	75.7*** (18.6)
	N85	65.0 (25.7)	69.4 (23.3)	76.1** (17.8)
NAW	Baseline	13.6 (4.8)	14.4 (4.6)	13.3 (4.3)
	N1	13.2 (5.5)	14.3 (6.4)	14.0 (6.2)
	N29	12.6 (5.0)	14.9* (5.9)	13.3 (5.2)
	N85	11.9 (5.3)	14.9** (6.6)	12.9 (5.6)
LPS (min) [Sleep onset]	Baseline	49.0 (27.3)	45.4 (25.3)	41.9 (22.7)
	N1	39.6 (29.3)	38..8(29.6)	28.6 (20.5)
	N29	39.1 (42.4)	49.2(51.2)	39.6 (40.0)
	N85	34.9 (33.0)	29.0 (26.5)	37.5 (32.7)

N=night; TST = Total Sleep Time; SE=Sleep Efficiency, NAW =number of awakenings after sleep onset, LPS+ latency to persistent sleep *P < 0.05 vs. placebo; **P < 0.01; ***P ≤ 0.0001.

Subjective Results:

Subjective Sleep Parameters		**Placebo (SD) n=81**	**Doxepin 1mg (SD) n=77**	**Doxepin 3mg (SD) n=82**
sTST (min)	Baseline	280.2 (87.9)	297.6 (73.3)	308.7 (80.9)
	Week 1	316.7 (68.3)	319.7 (84.6)	356.8** (61.1)
	Week 4	317.5 (83.2)	348.8*(60.3)	362.5** (65.4)
	Week 12	326.0 (77.9)	371.5** (59.8)	389.4*** (65.9)
Sleep Quality	Baseline	-0.1 (1.0)	0.0 (0.8)	0.1 (0.8)
	Week 1	0.0 (1.2)	0.2 (1.1)	0.6** (0.9)
	Week 4	0.1 (1.2)	0.5* (1.0)	0.7** (0.9)
	Week 12	0.2 (1.0)	0.8* (0.9)	0.9** (0.9)
CGI-Improvement	Baseline	3.6 (0.8)	3.7 (0.7)	3.7 (0.9)
	Week 1	3.2 (1.0)	3.2 (0.9)	27**0 (1.1)
	Week 4	2.6** (1.2)	2.7** (1.1)	2.8* (1.2)

	• 2 Likert scale prior to PSG assessing daytime function (1=extremely poor to 6= excellent) and drowsiness (1= extremely drowsy to 6 = extremely alert) during the preceding day. Next-day Residual: Objective: Digit Symbol Substitution Test (DSST) and Symbol Copying Test (SCT) and Subjective:100 mm visual analog scale (VAS) Safety: laboratory test (hematology, serum chemistry, UA), VS, 12-lead ECG and PE	

	Week 12	11.9 (5.3)	14.9** (6.6)	2.4*** (1.1)
Insomnia Severity Index	Baseline	15.4 (3.8)	14.3 (4.4)	15.1 (3.8)
	Week 1	14.0 (4.2)	12.9 (4.4)	12.5* (4.6)
	Week 4	13.5 (4.0)	12.0 (4.3)	11.6** (4.9)
	Week 12	13.0 (4.9)	10.9 (4.9)	10.6** (4.7)

SD= Standard deviation, sTST= Subjective Total Sleep Time; Sleep Quality scale from -3 to 3; -3 extremely poor to 3= excellent.

Early morning awakenings: SE in the last quarter of the night was significantly increased on N1 ($p < 0.0001$), N29 ($p = 0.0001$), and N85 ($p = 0.0014$) for DXP 3mg. For DXP 1mg, SE in the last quarter of the night was significantly increased on N1 ($p = 0.0011$). SE in hour 8 was significantly increased on N1 ($p < 0.0001$) and N29 ($p = 0.0029$) but not N85 for doxepin 3mg. For doxepin 1 mg, SE in hour 8 was significantly increased only on N1 ($p = 0.0211$). WTAS was significantly decreased on N85 ($p = 0.00284$ for DP 3mg compared to placebo.

Sleep Quality: Sleep quality was significantly increased at Weeks 1 ($p=0.0019$), 4 ($p = 0.0049$), and 12 ($p=0.0100$) for DXP 3 mg and at Weeks 4 ($p = 0.0464$) and 12 ($p = 0.0107$) for DXP 1mg.
Clinical Global Insomnia Outcomes: Significant improvement on the CGI Severity scale score was seen only for DXP 3mg across all weeks compared to placebo. CGI Improvement scores statistically improved with 3mg for Weeks 2, 4, and 12 and with 1mg for Week 12.
Patient Global Insomnia Outcomes: All 5 of the 5 items improved with both doses of DXP compared to placebo by Week 12.
Insomnia Severity Index: DXP 3mg but not DXP 1mg significantly improved the ISI score for Weeks 1, 4, and 12 compared to placebo.
Sleep architecture: DXP 3 and 6 mg increased the duration of Stage 2.
Safety:
Treatment Emergent Adverse Events: 52% placebo; 40% DXP1mg; 18% in DXP 6mg.The most common AEs reported headache and somnolence.
Discontinuation Rates: 14% placebo; 9% DXP 1mg, 10% DXP 3mg. Withdrawn due to AEs: 4%, 1%, 4% in placebo, DXP 1mg and DXP 3mg, respectively.
Next-day Residual Effects: No significant differences between placebo and either dose of DXP on any objective psychomotor functions (DSST and SCT) and subjective next-day alertness (VAS) or drowsiness at any time point during the trial.

Conclusions:
- DXP 3 mg statistically improved sleep maintenance (WASO) on N1 (primary endpoint) thru N85 compared to placebo in the elderly. DXP 1mg significantly improved WASO on N1 and N85 compared to placebo.
- DXP1 mg statistically improved TST compared to placebo on N1 and N85. DXP 3 mg was superior to placebo for TST for all nights.
- Significant early morning awakenings reductions as measured by sleep efficiency % in the last quarter of the night was seen with DXP 3 mg on N1, N29, and N85 and for DXP 1 mg on N1.
- Clinical Global Insomnia Outcomes (Severity and Improvement) scores improved with DXP on weeks 1, 4, and 12.

Randomized; DB = double-blind; PC = placebo-controlled; MC = multicenter; LPS= Latency to persistent sleep; PE= physical exam; VS= vital signs; PSG= polysomnography; TST = Total Sleep Time; ECG= Electrocardiogram

		• Insomnia Severity Index improved with DXP 3mg on Weeks 2, 4, and 12 • No significant differences in next-day hangover/residual seen with either doses of DXP compared to placebo • Both doses of DXP were well tolerated. Vital signs, ECG, PE and clinical laboratory values were comparable across the three groups. (data not shown) • No reports of complex sleep behaviors, memory impairment, or cognitive disorders in any DXP-treated subjects. **Quality Assessment:** Good (although may not be generalized to the VA as the study patients were "generally healthy elderly adults". Study Critique: • Strength: R, DB study; primary endpoint achieved statistical significance; objective and subjective sleep parameters evaluated • Weakness: Objective measures of daytime functions were not studied. Rebound insomnia or withdrawal symptoms were not studied. • Limitations: Population was limited to primary insomnia patients so results may not be applied to patients with co-morbidities or to the VA population. Highest approved DXP dose (6 mg) was not studied in the elderly population. Tolerance was not addressed although the mean WASO although significant to placebo, declined from N 29 to N85 (84.3 to 75.7 minutes) with DXP 3mg. Mean WASO increased 0.6 minutes from N29 to N85 with DXP 1mg. Preparation and publication of article was supported by Somaxon Pharmaceuticals, 4/7 authors were employees of Somaxon. Remaining three authors received financial support from company.

R=randomized; DB= double-blind; PC= placebo-controlled; MC=multicenter; PE= physical exam; VS= vital signs; LPS= Latency to persistent sleep; NAASO: number or awakenings after sleep; WTDS=wake time during sleep

Table 3: Low –Dose Doxepin Responses Compared to Placebo on Sleep Maintenance Outcomes*

Population (Author, Date) N	Duration of effect	Outcome Variables	Mean difference low-dose doxepin vs placebo on sleep maintenance outcomes (95% CI); p value		
			DXP 1mg	DXP 3mg	DXP 6mg
Adult Primary Insomnia Patients (Krystal, 2011) N=229	Night 1	PSG WASO	-	-25.4 (-34.9, -9.5); 0.0002	-30.5 (-43.4, -17.6); <0.0001
		PSG TST	-	41.4 (22.4, 60.4); <0.0001	48.6 (28.1. 65.1); <0.0001
		PSG SE (last quarter)	-	8.4 (2.8, 14.0); 0.003	9.9 (4.8, 15.1) ; 0.0002
	Night 15	PSG WASO	-	-15.8 (-29.4, -2.2); 0.02	-18.8 (-32.5, -5.1); 0.007
		PSG TST	-	12.9 (-5.5, 31.3); 0.17	22.2 (3.7, 40.7); 0.02
		PSG SE (last quarter)	-	5.4 (0.1, 10.8); 0.048	6.2 (1.0, 11.4); 0.02
	Night 29	PSG WASO	-	-13.3 (-26.6, -0.02); 0.049	-19.8 (-32.2, -7.5); 0.0002
		PSG TST	-	16.5 (0.01-33.0); 0.05	28.0 (12.9, 43.1); 0.0003
		PSG SE (last quarter)	-	4.4 (0.6, 9.4); 0.08	7.1 (2.1, 12.1); 0.005

Adults Primary Insomnia Patients (Roth, 2007) N=67	Night 1	PSG WASO	-14.4 (-27.6, -1.2); 0.03	-22.2 (-34.9, -9.5); 0.0006	-23.0 (-35.6; -10.4); 0.0003
		PSG TST	17.9 (3.3, 32.5); 0.02	25.8 (11.4, 40.2); 0.0005	28.8 (14.7, 42.9); <0.0001
		PSG SE	3.7 (0.7, 6.7); 0.02	5.3 (2.3,8.3); 0.0006	6.0 (3.1, 8.9); <0.0001
Adults with Induced Transient Insomnia (Roth,2010) N=565	Night 1	PSG TST	-	-	51.1 (41.8, 60.5); <0.0001
		PSG SE (last quarter)	-	-	10.4 (7.4, 13.4); <0.0001
		PSG SE	-	-	10.7 (8.8, 12.7); <0.0001
		sTST	-	-	33.1 (22.4, 43.8); <0.0001
		sSQ	-	-	0.4 (0.2, 9.6); <0.0001
Elderly Primary Insomnia Patients (Krystal, 2010) N= 240	Night 1	PSG WASO	-17.1 (-31.6, -2.6); 0.02	-34.4 (-47.4, -21.5); <0.0001	-
		PSG TST	19.4 (2.6, 36.2); 0.02	43.2 (28.0, 58.4); <0.0001	-
		PSG SE (last quarter)	10.4 (3.6, 7.2); 0.0003	14.5 (8.1, 20.9); <0.0001	-
	Night 7	sTST	3.5 (-23.4, 30.4); 0.30	40.6 (18.1. 63.1); 0.0004	-
		sSQ	0.2 (-0.2, 0.6); 0.33	0.6 (0.2, 1.0); 0.0001	-
	Night 29	PSG WASO	-8.2 (-23.6, 7.2); 0.30	-20.3(-34.9, -5.7); 0.0007	-
		PSG TST	-0.6 (-18.4, 17.2); 0.95	18.9 (1.5, 36.3); 0.03	-
		PSG SE (last quarter)	3.5 (-3.9, 10.9); 0.35	11.0 (4.3, 17.8); 0.001	-
		sTST	31.3 (5.8, 56.8); 0.02	45.0 (19.0, 71.0); 0.0007	-
		sSQ	0.4 (0.01, 0.8);0.04	0.6 (0.3, 0.9); 0.0004	-
	Night 85	PSG WASO	-12.2 (-27.0, 2.6); 0.11	-33.5 (-47.2, 19.8); <0.0001	-
		PSG TST	16.8 (0.4, 33.2); 0.04	30.0 (14.5, 45.5); 0.0002	-
		PSG SE (last quarter)	4.4 (-3.2, 12.0); 0.26	11.1 (4.3, 17.9); 0.001	-
		sTST	45.5 (21.1, 69.9); 0.0003	63.4 (38.3, 88.5); <0.0001	-
		sSQ	0.6 (0.3, 0.9); 0.0004	0.7 (0.4, 1.0); <0.0001	-

Elderly Primary Insomnia (Lankford, 2011) n=254	Night 7	sWASO	-	-	-18.3 (-30.5, -6.1); 0.003
		sTST	-	-	18.5 (4.1, 32.9); 0.01
		sSQ	-	--	0.5 (0.3, 0.8); 0.001
	Night 29	sWASO	-	-	-12.4 (-24.9, 0.1); 0.05
		sTST	-	-	9.7 (-6.4, 25.8); 0.24
		sSQ	-	-	0.2 (-0.1, 0.5); 0.13
Elderly Patients with Primary Insomnia (Scharf, 2008) n= 76	Night 1	PSG WTDS	-16.2 (-27.7, 4.7); 0.006	-21.0 (-32.4, -9.6); 0.0003	-17.5 (-37.2, -15.4); <0.0001
		PSG NAASO	0.2 (-1.3, 1.7); 0.80	0.6 (-1.0, 2.2); 0.46	0.6 (-0.9, 2.1); 0/.49
		PSG SE	3.5 (0.7, 6.3); 0.01	6.3 (3.4, 9.2); <0.0001	7.9 (5.3, 10.5); <0.0001
		PSG TST	16.7 (3.5, 29,9); 0.01	29.9 (16.2, 43.7); <0.0001	37.7 (25.2, 50.2); <0.0001
		sTST	16.6 (-5.3, 38.5); 0.14	24.2 (2.1, 46.3) 0.03	30.8 (8.7, 52.9); 0.006
		sSQ	0.20 (-o.11, 0.51); 0.21	0.40 (0.09, 0.71); 0.01	0.40 (0.09, 0.71); 0.01
		sWASO	-15.2 (-34.1, 3.7); 0.12	-20.0 (-39.1, -0.9); 0.04	-19.1 (-38.3, 0.1); 0.05

*Adapted from Reference #3.