Doxepin in the Treatment of Primary Insomnia: A Placebo-Controlled, Double-Blind, Polysomnographic Study

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Background: Over recent years, the use of antidepressants for the symptomatic treatment of insomnia has grown substantially, but controlled studies are still lacking. Our study is the first investigation to prove objective efficacy and tolerability of low doses of a sedating antidepressant in a randomized, double-blind, and placebo-controlled manner in patients with primary insomnia.

Method: Forty-seven drug-free patients meeting DSM-IV criteria for primary insomnia (mean ± SD duration of complaints = 11.2 ± 9.7 years) received either 25–50 mg of the tricyclic antidepressant doxepin or placebo for 4 weeks followed by 2 weeks of placebo withdrawal. Sleep was measured by polysomnography at baseline and the first night of application, at 4 weeks of treatment and the first to third night of withdrawal, and after 2 weeks of withdrawal.

Results: In the doxepin-treated patients who completed the study (N = 20, 47.6 ± 11.3), medication significantly increased sleep efficiency after acute (night 1, $p \leq .001$) and subchronic (night 28, $p \leq .05$) intake compared with the patients who received placebo (N = 20, 47.4 ± 16.8 years of age). Latency to sleep onset was not affected since the patients had normal baseline sleep latencies. Investigators found doxepin to cause significantly ($p \leq .05$) better global improvement at the first day of treatment. Patients rated sleep quality ($p \leq .001$) and working ability ($p \leq .005$) to be significantly improved by doxepin during the whole treatment period. Overall rebound in sleep parameters was not observed, but patients with severe rebound insomnia were significantly more frequent in the doxepin group (night 29, $p \leq .01$; night 30, $p \leq .01$; night 31, $p \leq .05$). No significant group differences in side effects were found, but 2 doxepin-treated patients dropped out of the study due to specific side effects (increased liver enzymes, leukopenia, and thrombopenia).

Conclusion: The results support the effectiveness of low doses of doxepin to improve sleep and working ability in chronic primary insomniacs, although subjective effects were light to moderate, and in some patients, rebound insomnia and specific side effects have to be considered.

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In industrial countries worldwide, up to one third of the population reports at least occasional difficulties with sleep, particularly insomnia.[1–6] Insomnia is defined as a difficulty to initiate or maintain sleep, resulting in a nonrefreshing or nonrestorative sleep.[7–9] About three quarters of the insomniac patients are afflicted chronically, suffering from their complaints for years or even decades.[10–13] Patients with chronic insomnia demonstrate increased social impairment, stress, medical illness, and fatigue-related automobile accidents when compared with good sleepers.[14,15] Health costs in the United States for the treatment of insomnia in 1990 were estimated at $10.9 billion[16] and the loss of productivity due to insomnia in the United States was estimated to be $41.1 billion in 1998.[17] Depending on the country, approximately 3% to 10% of the population use sleep-promoting medication.[18–23] Worldwide, hypnotics acting at the benzodiazepine receptor site (benzodiazepines, cyclopyrrolones, imidazopyridines) have been the most frequently applied drugs to combat disordered sleep. Their use has been documented to be effective for the short-term (i.e., a few days or a few weeks) management of insomnia, while long-term medication has not been studied systematically and appears to be of little benefit for the patients.[11,24] Primarily, the uncritical use of hypnotics has raised the issue of whether benzodiazepine receptor agonists have a favorable benefit/risk ratio in the treatment of chronic insomnia. Aside from their potential for abuse, benzodiazepines[25–29] and, to a lesser extent, other medications acting on the same receptor system[30–32] have been shown to promote the risk of addiction. Increasing awareness of the resulting problematic efficacy/side effect ratio

has stimulated the search for alternative sleep-promoting agents. Sedating tricyclic antidepressants (TCAs) (e.g., amitriptyline, trimipramine, doxepin) and atypical antidepressants (e.g., trazodone, nefazodone, mirtazapine) are considered to be major candidates.[33–37]

A large number of studies have proven antidepressants to increase sleep efficiency and slow wave sleep and to reduce latency to sleep onset in healthy subjects as well as in patients with depression even after long-term application.[38–49] Antidepressants also seem to have low potential for abuse and dependence. While withdrawal phenomena may occur in a few cases, they do not reach the strength of withdrawal symptoms found after abrupt discontinuation of long-term benzodiazepine receptor agonist usage.[50–54]

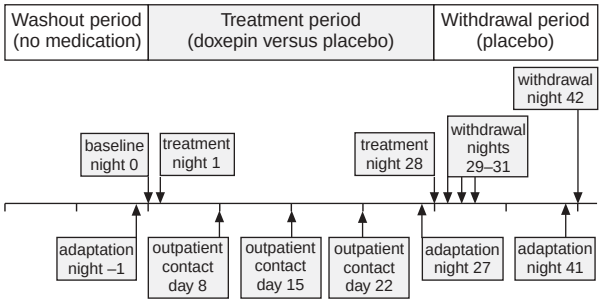
Up to now, 1 placebo-controlled double-blind study (trazodone, 50 mg, N = 278, subjective sleep measures), 1 single-blind study (trimipramine, 75–200 mg, N =15, subjective and polysomnographic sleep measures), and 2 open studies (doxepin, 25 mg, N = 10, subjective and polysomnographic sleep measures; paroxetine, 5–30 mg, N = 14, subjective and polysomnographic sleep measures) have investigated antidepressants as hypnotic drugs in insomniac patients without concomitant or underlying psychiatric disease, e.g., depression. In these studies, trazodone,[55] trimipramine,[35] doxepin,[34] and even the nonsedating paroxetine[56] provided remarkable sleep-improving effects. These promising results have been paralleled by the increasing use of antidepressants for the treatment of sleep complaints in general practice.[4,57,58] In the United States from 1987 to 1996, the prescription rate of antidepressants for the treatment of insomnia increased by 146%, while benzodiazepine hypnotics fell by 53.7%.[36] However, general use of antidepressants as hypnotic drugs is still disputed, due to the lack of controlled studies concerning both the efficacy on sleep measures and the risk of side effects in insomniac patients. We therefore investigated the effects of 4 weeks of treatment with the TCA doxepin on objective and subjective sleep parameters in patients with primary insomnia following a double-blind and placebo-controlled design.

METHOD

Patients

Forty-seven patients (mean ± SD age = 47 ± 11 years; 11 men, 36 women) from the Sleep Disorders Centers at the Departments of Psychiatry of the Universities of Göttingen and Freiburg, Germany, participated in the study. All patients suffered from primary insomnia according to the criteria of the Fourth Revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).[7] They also fulfilled the criteria of a psychophysiologic insomnia following the International Classification of Sleep Disorders (ICSD).[8] Diagnoses were made by physicians who were specialized in neurology and psychiatry and have been qualified as sleep experts by the German Sleep Society. The patients were chronically ill and had suffered from sleep problems (mainly difficulties in maintaining sleep) for 11.2 ± 9.7 years. Acute, chronic, and recurrent somatic and psychiatric disorders were excluded by physical examination, routine laboratory tests, electrocardiogram (ECG), electroencephalogram (EEG), and a semistructured interview. Sleep disorders other than primary insomnia were excluded by interview and polysomnography. Urine toxicology was performed for benzodiazepines and drugs of abuse. All subjects were free of psychotropic medication including hypnotics at least 2 weeks before the start of the study. Patients gave their written informed consent after study procedures and possible side effects were fully explained. The study was approved by the local ethics committees.

Figure 1. Study Design Used to Measure the Effects of Doxepin on Sleep



Study Design

A randomized, double-blind, and placebo-controlled design was used to measure effects of doxepin on sleep (Figure 1). Patients received either placebo over the whole investigation period of 6 weeks (placebo group) or 25 mg or 50 mg doxepin for 4 weeks followed by 2 weeks of placebo intake (doxepin group). Medication was given orally 1 hour before estimated bedtime. All patients received 1 capsule of the study medication (placebo or 25 mg doxepin) during the first week of treatment. In cases of subjective ineffectiveness (according to the decision of the patient), the study dose was enhanced and patients received 2 capsules (50 mg doxepin or placebo) starting from day 8 until the end of the treatment period. Placebo medication was continued with a corresponding number of capsules until the end of the study. Polygraphic sleep recordings were performed in 3 sessions: (1) at baseline (night 0) and the first medication intake (night 1), (2) at 4 weeks of treatment (night 28) and the first to third night of placebo withdrawal (nights 29 to 31), and (3) at the end of the placebo withdrawal 2 weeks after discontinuation of active treatment (night 42). Each of the 3 polysomno-

graphic sessions was preceded by an adaptation night in the sleep laboratory. Items from the Clinical Global Impressions Observer Rating Scale[59] were rated 14 days before starting the study, after each polysomnography, and at all outpatient visits. Subjective sleep quality and daytime performance were assessed daily using visual analogue scales[60] during the whole investigation period.

Sleep EEG Recordings

Sleep was recorded at sleep laboratories of the 2 participating centers (Göttingen, Freiburg) in agreement with standard recommendations.[61,62] Sleep measurements included EEG (C4 scalp placement according to the 10–20 EEG system), electrooculogram, and submental chin electromyogram (EMG). During the first adaptation night, polysomnography included recording of the respiratory function and EMG of the anterior tibialis muscles to screen for sleep apnea syndrome (apnea-hypopnea index > 10/hour sleep) and periodic limb movement disorder (periodic-limb movement-arousal index > 10/hour sleep). All patients were recorded starting within 30 minutes of their habitual bedtime as determined by sleep questionnaires. All sleep recordings were analyzed at 1 study center (Göttingen) and scored visually according to standard criteria.[62] In particular the following sleep parameters were evaluated:

- Global parameters: time in bed (TIB), sleep period time (SPT, time from sleep onset to final awakening), total sleep time (TST), sleep efficiency (SE, ratio of TST to TIB × 100)
- Parameters of sleep architecture: amount of wake after sleep onset (WASO), sleep stages I, II, slow wave sleep (SWS), and rapid eye movement (REM) expressed in percent of SPT
- Latencies: Sleep onset latency (SL, time from lights off to the first epoch of sleep stage II), REM latency (REM-L, time from sleep onset to the first epoch of stage REM), SWS latency (SWS-L, time from sleep onset to the first epoch of SWS).

Investigator Ratings

Parts from the Clinical Global Impressions Observer Rating Scale (CGI)[59] including the items "severity of illness" and "global improvement" were rated by the investigators 14 days before baseline, at baseline, after each polysomnographic night, and at all outpatient visits, which were performed weekly between baseline and day 28.

Patients' Self-Ratings

Subjective sleep quality and daytime performance, i.e., working ability and energy, were assessed by the patients daily using visual analogue scales (VAS) obtained from VIS-A and VIS-M scales.[60] In order to eliminate day-to-day variability, evaluation of these parameters was based on mean values obtained over 2-week periods: (1) the last 2 weeks before baseline, (2) the first and (3) the last 2 weeks of the double-blind period, and (4) the 2 weeks of the single-blind discontinuation of active treatment.

Rebound

Rebound effects, i.e., the deterioration of sleep parameters to below individual pretreatment values (no-pill baseline),[63–65] were assessed for the sleep parameters with significant changes during the treatment period (SE, TST, WASO, sleep stage II percentages). In order to investigate short-term and long-term withdrawal effects, rebound was evaluated for each of the 3 nights of acute withdrawal (short-term rebound; nights 29–31) and after 2 weeks of withdrawal (long-term rebound; night 42). The rebound analysis compared the mean changes of the sleep parameters SE, TST, WASO, and sleep stage II percentages from baseline values of both groups. A further detailed rebound analysis calculated the number of patients suffering from rebound (rebound rate) in at least 1 up to all 4 of the rebound sleep parameters.[66] Finally, the mean changes in rebound sleep parameters in these patients with rebound were calculated.

Side Effects

Side effects were monitored weekly by interview and by using a standardized symptom checklist (Fischer Somatic or Undesired Effects Check-List [FSUCL][67]), which includes 26 side effect items divided into 6 groups:

- symptoms of the central nervous system: 5 items, e.g., tiredness, agitation, sleep disorders;
- symptoms of the autonomic nervous system: 5 items, e.g., mouth dryness, sweating;
- gastrointestinal functions: 6 items, e.g., increased/decreased appetite, vomiting;
- circulatory functions: 2 items, dizziness, hypotension;
- headache: 1 item;
- neurologic symptoms: 7 items, e.g., hypo/hyperkinesia, cramps.

Statistics

All results were expressed as mean values ± standard deviation. For inferential statistics, analysis of variance (ANOVA) with repeated measurements (sleep parameters, scores from CGI and VAS) was calculated separately for each parameter followed by Duncan tests if p values for the treatment × night interaction were below .05. Rebound rates and side effects were analyzed by chi-square tests. Student t tests were used to estimate group differences concerning the amount of rebound effects. Significant outcomes were alpha-adjusted using the method of Cross and Chaffin.[68]

Table 1. Reasons for Dropout During Treatment of Patients With Primary Insomnia[a]

No.	Sex	Day of Dropout	Group	Dosage (mg/d)	Reasons for Dropout
1	Female	8	Doxepin	25	Exanthema, gastric disorder, dizziness
4	Male	22	Placebo		Nervousness, gastric disorder, feeling of coldness
18	Male	24	Doxepin	25	Dizziness, headache, common cold, disturbed accommodation, increased liver enzymes (alanine aminotransferase 256 U/L, γ-glutamyl transferase 156 U/L)
22	Female	9	Doxepin	25 (1 × 50 mg)	Leukopenia (3.5×10^9/L), thrombopenia (107×10^9/L), headache, orthostatic hypotension
41	Female	1	Placebo		Protocol failure during run-in period
43	Male	15	Doxepin	25	Personal reasons
47	Female	15	Placebo		Constipation

[a]Total number of patients = 47; number of dropouts = 7; patients in study = 40.

Table 2. Severity of Illness and Global Improvement According to Clinical Global Impressions Observer Rating Scale (CGI)[59] After Doxepin (N = 20) and Placebo (N = 20) Treatment and Withdrawal in Primary Insomnia

	Group, Mean ± SD										
	Baseline		Treatment					Withdrawal			
	–14	0	1	8	15	22	28	29	30	31	42
Severity of illness[a]											
Placebo	4.90 ± 0.72	4.55 ± 0.76	4.70 ± 0.57	4.40 ± 0.88	4.25 ± 0.91	4.10 ± 0.79	3.85 ± 0.93	4.10 ± 0.64	3.90 ± 0.85	4.20 ± 0.62	3.95 ± 0.76
Doxepin	4.55 ± 0.69	4.50 ± 0.76	4.05 ± 0.94	3.90 ± 0.97	3.75 ± 1.02	3.70 ± 1.22	3.50 ± 1.10	3.75 ± 1.16	3.75 ± 0.91	4.15 ± 0.33	3.80 ± 1.15
Global improvement[b]											
Placebo			3.89 ± 0.90	3.28 ± 0.96	2.78 ± 1.06	2.94 ± 0.64	3.00 ± 0.69	3.39 ± 0.98	2.67 ± 0.97	3.00 ± 0.77	2.72 ± 0.89
Doxepin			3.16 ± 0.76	3.16 ± 0.90	2.79 ± 0.92	2.42 ± 0.91	2.42 ± 0.77	3.11 ± 1.05	3.11 ± 1.29	3.37 ± 1.26	2.84 ± 1.07

[a]Severity of illness scale included the values 0 (not assessed) and 1 (normal, not at all ill) to 7 (among the most extremely ill patients).
[b]Global improvement scale included the values 0 (not assessed) and 1 (very much improved) to 7 (very much worse).

RESULTS

Patients

Seven patients did not complete the study due to side effects (5 patients), personal reasons (1 patient), or protocol violation (1 patient). Four patients of the doxepin group and 3 patients of the placebo group dropped out. Dropout patients of the doxepin group showed more severe side effects such as increased liver enzymes, exanthema, and leukopenia than dropout patients of the placebo group (Table 1).

The remaining 40 patients were included in the data analysis. A total of 20 patients (5 male, 15 female, 47.4 ± 16.8 years of age, duration of insomnia: 10.5 ± 8.3 years) received placebo. Twenty patients (3 male, 17 female, 47.6 ± 11.3 years of age, duration of insomnia: 10.7 ± 10.3 years) were treated with 25 mg (N = 9) or 50 mg (N = 11) of doxepin.

Patients treated in this study were moderately to markedly ill as suggested from baseline CGI ratings. Severity of illness was 4.55 ± 0.76 in the placebo group and 4.50 ± 0.76 in the doxepin group (Table 2). This moderate-to-marked sleep disturbance was paralleled by objective sleep parameters with baseline values of sleep efficiency of 81.29% ± 12.94% (placebo group) and 78.42% ± 14.59% (doxepin group) or wake time after sleep onset of 13.04% ± 10.56% (placebo group) and 17.02% ± 15.37% (doxepin group) from sleep period time (Table 3).

Polygraphic Sleep Parameters

A total of 280 of 400 (adaption nights + measurement nights) polysomnographically recorded nights were included in the statistics of the sleep parameters. ANOVA revealed significant treatment × night interactions for TST ($F = 4.87$, $p \leq .001$), SE ($F = 5.37$, $p \leq .001$), stage II percentages ($F = 5.52$, $p \leq .001$), and WASO ($F = 3.63$, $p \leq .01$). Significant treatment effects occurred only in the doxepin group. Placebo failed to change any sleep parameter (Table 3).

Subsequent Duncan tests showed that SE was significantly higher in the doxepin group than in the placebo group after both acute (night 1, $p \leq .001$) and subchronic (night 28, $p \leq .05$) doxepin intake (Figure 2). After the first night with doxepin (night 1), TST ($p \leq .01$, Figure 3) and sleep stage II percentages ($p \leq .01$, Figure 4) were significantly increased and WASO was decreased ($p \leq .01$, Figure 5) compared with placebo treatment. SE ($p \leq .001$), TST ($p \leq .01$), WASO ($p \leq .01$), and sleep stage II percentages ($p \leq .05$) were also significantly different from baseline (night 0) at night 1 and night 28 of the doxepin administration (Figures 2–5).

Detailed Duncan analysis further displayed significantly lower values of TST ($p \leq .01$) and SE ($p \leq .05$) after acute doxepin withdrawal (night 29) compared with the placebo group, but no impairments compared with baseline (Figures 2 and 3). Percentages of sleep stage II were significantly decreased ($p \leq .05$) in the doxepin group dur-

Table 3. Sleep Parameters After Doxepin (N = 20) and Placebo (N = 20) Treatment and Withdrawal in Primary Insomnia[a]

Time	Group, Mean ± SD											
	TIB, min	SPT, min	TST, min	SE, %	SL, min	SWS-L, min	REM-L, min	Stage I, % SPT	Stage II, % SPT	SWS, % SPT	REM, % SPT	WASO, % SPT
Night 0 baseline												
Placebo	495.25 ± 57.11	460.85 ± 56.30	398.95 ± 61.77	81.29 ± 12.94	20.65 ± 24.96	43.98 ± 97.65	74.05 ± 40.38	7.20 ± 2.94	53.87 ± 9.59	5.51 ± 4.18	20.27 ± 4.13	13.04 ± 10.56
Doxepin	483.88 ± 30.32	458.05 ± 32.69	378.88 ± 70.02	78.42 ± 14.59	16.28 ± 10.70	51.75 ± 111.34	98.05 ± 73.84	8.78 ± 5.59	49.34 ± 10.02	7.22 ± 6.02	17.44 ± 6.27	17.02 ± 15.37
Night 1 treatment												
Placebo	493.20 ± 51.90	459.25 ± 54.41	384.18 ± 64.96	78.04 ± 12.07	21.35 ± 16.29	48.68 ± 99.75	70.50 ± 28.34	7.23 ± 3.07	50.88 ± 8.91	5.56 ± 5.02	19.83 ± 4.51	16.24 ± 11.27
Doxepin	486.23 ± 45.07	467.28 ± 47.32	431.63 ± 44.71	88.93 ± 6.36	15.88 ± 15.79	78.30 ± 160.15	101.58 ± 45.59	10.19 ± 7.19	58.26 ± 5.99	8.63 ± 8.00	16.49 ± 6.49	7.43 ± 5.76
Night 28 treatment												
Placebo	493.35 ± 43.86	469.73 ± 45.13	408.20 ± 74.35	82.84 ± 14.02	17.43 ± 15.11	68.20 ± 130.55	62.04 ± 28.13	7.63 ± 2.66	53.12 ± 9.23	5.42 ± 5.07	20.69 ± 6.60	12.97 ± 14.24
Doxepin	483.90 ± 31.63	465.98 ± 39.03	430.25 ± 43.58	88.85 ± 5.81	12.93 ± 7.62	43.93 ± 92.57	88.03 ± 34.12	10.94 ± 6.88	55.06 ± 6.43	7.08 ± 5.95	18.98 ± 5.41	7.68 ± 4.99
Night 29 withdrawal												
Placebo	491.56 ± 56.37	470.53 ± 57.56	414.64 ± 37.32	85.11 ± 9.69	14.58 ± 12.02	81.97 ± 143.56	72.81 ± 40.65	9.26 ± 4.92	53.38 ± 8.07	4.62 ± 4.16	21.49 ± 3.90	11.07 ± 9.36
Doxepin	472.28 ± 64.63	442.83 ± 56.33	368.68 ± 87.44	78.34 ± 16.90	22.38 ± 26.63	69.33 ± 130.20	86.43 ± 64.38	10.85 ± 4.38	46.75 ± 10.78	6.81 ± 4.98	18.90 ± 7.69	16.77 ± 16.13
Night 30 withdrawal												
Placebo	483.40 ± 49.94	450.33 ± 62.63	392.20 ± 74.65	81.34 ± 13.72	22.65 ± 21.52	59.23 ± 91.50	67.43 ± 48.15	8.04 ± 3.11	52.28 ± 9.11	5.95 ± 4.29	20.69 ± 4.50	12.87 ± 11.69
Doxepin	466.66 ± 39.24	413.14 ± 106.75	369.79 ± 67.60	79.23 ± 12.62	29.68 ± 29.84	59.97 ± 108.12	67.16 ± 25.94	10.29 ± 6.00	46.47 ± 7.80	8.52 ± 6.87	20.01 ± 5.69	14.29 ± 13.12
Night 31 withdrawal												
Placebo	470.78 ± 41.28	435.95 ± 39.99	389.48 ± 55.17	83.39 ± 13.30	24.40 ± 40.48	76.73 ± 137.96	62.15 ± 42.34	8.57 ± 3.83	52.74 ± 8.80	6.04 ± 4.82	21.67 ± 2.64	10.64 ± 9.11
Doxepin	458.35 ± 45.31	430.98 ± 45.83	371.45 ± 45.93	81.33 ± 8.94	17.05 ± 9.39	64.93 ± 123.33	76.58 ± 60.81	10.43 ± 4.91	46.45 ± 8.87	7.32 ± 5.86	22.00 ± 5.29	13.17 ± 7.94
Night 42 withdrawal												
Placebo	479.80 ± 66.28	449.83 ± 64.00	390.90 ± 61.67	82.66 ± 14.99	17.40 ± 23.95	83.25 ± 142.92	72.06 ± 62.14	7.45 ± 3.26	52.85 ± 12.51	6.36 ± 5.71	20.86 ± 4.54	12.29 ± 14.02
Doxepin	461.68 ± 47.61	435.23 ± 58.05	397.50 ± 58.03	85.94 ± 6.88	13.85 ± 8.09	51.93 ± 113.83	77.38 ± 40.47	8.81 ± 4.66	52.56 ± 5.76	8.92 ± 7.04	20.87 ± 4.35	8.55 ± 6.10

[a]Abbreviations: REM = rapid eye movement; REM-L = REM latency; SE = sleep efficiency; SL = sleep onset latency; SPT = sleep period time; SWS = slow wave sleep; SWS-L = SWS latency; TIB = time in bed; TST = total sleep time; WASO = wake after sleep onset.

ing all active withdrawal nights (nights 29–31) compared with baseline (Figure 4). After 2 weeks of withdrawal, SE ($p \leq .05$, Figure 2) and WASO ($p \leq .01$, Figure 5) were significantly improved compared with baseline.

Beside the significant changes, doxepin and placebo tended to reduce latency to sleep onset after 4 weeks of treatment. There was also a tendency for an increase in sleep stage I percentages during active treatment and withdrawal compared with baseline. Sleep latency and slow wave sleep latency were somewhat prolonged during acute withdrawal compared with baseline. REM latency was not affected by doxepin after acute administration nor at the end of the 4-week period (Table 2).

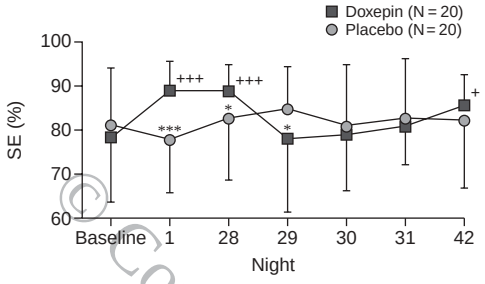
Investigators' Ratings

Concerning severity of illness and global improvement from the CGI scale performed by the investigators, ANOVA revealed a significant treatment × time interaction ($F = 2.3768$, $p \leq .05$) for global improvement (Table 2). Detailed analysis showed that acute doxepin reduced patients' insomnia immediately at day 1 compared with placebo ($p \leq .05$) (Table 2). Severity of illness was reduced in both groups in the course of treatment ($F = 10.2919$, $p \leq .001$), but ANOVA failed to detect significant treatment × time interactions (Table 2).

Patients' Self-Ratings

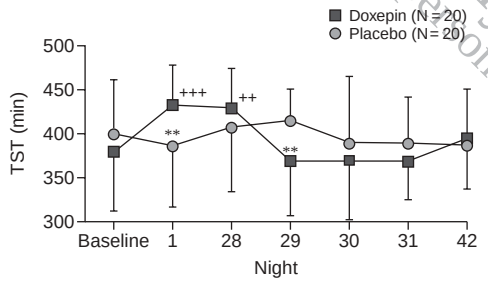
With regard to subjective assessments of sleep and daytime performance by the patients on visual analogue scales, ANOVA showed significant treatment × time interactions for sleep quality ($F = 6.1472$, $p \leq .001$) and working ability ($F = 3.4058$, $p \leq .005$). Subsequent Duncan tests showed that sleep quality was significantly increased during the whole active doxepin treatment period compared with placebo (Figure 6). Doxepin further increased sleep quality significantly, compared with the pretreatment value (Figure 6). Working ability was significantly higher during active doxepin treatment and discontinuation compared with placebo (Figure 7). Within the doxepin group, working ability was significantly increased in the last 2 weeks of treatment compared with pretreatment (Figure 7). ANOVA revealed no significant treatment × time interactions for the item "energy." Doxepin tended to improve energy (pretreatment, 55.02 ± 11.11 mm; first 2 weeks of treatment, 48.73 ± 15.65 mm; last 2 weeks of treatment, 46.20 ± 16.90 mm; discontinuation, 46.44 ± 16.42 mm), while placebo failed to change this item (pretreatment, 58.99 ± 10.50 mm; first 2 weeks of treatment, 56.03 ± 13.88 mm; last 2 weeks of treatment, 57.80 ± 11.38 mm; discontinuation, 54.05 ± 11.53 mm).

Figure 2. Sleep Efficiency (SE) After Doxepin and Placebo Administration Over 4 Weeks (nights 1 to 28) and Placebo Withdrawal (nights 29 to 42) in Patients With Primary Insomnia



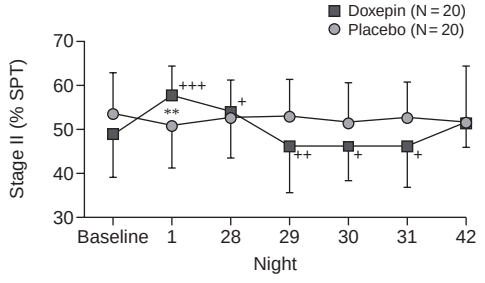
***p < .001, group comparison.
*p < .05, group comparison.
+++p < .001 compared with baseline within the doxepin group.
+p < .05 compared with baseline within the doxepin group.

Figure 3. Total Sleep Time (TST) After Doxepin and Placebo Administration Over 4 weeks (nights 1 to 28) and Placebo Withdrawal (nights 29 to 42) in Patients With Primary Insomnia



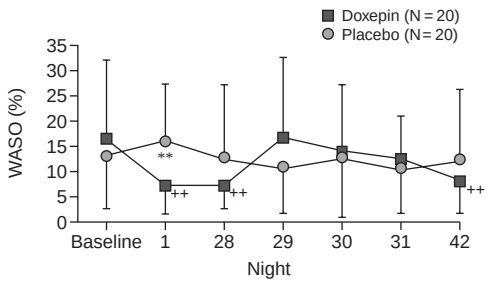
**p < .01, group comparison.
+++p < .001 compared with baseline within the doxepin group.
++p < .01 compared with baseline within the doxepin group.

Figure 4. Stage II Percentages From Sleep Period Time (Stage II, % SPT) After Doxepin and Placebo Administration Over 4 Weeks (nights 1 to 28) and Placebo Withdrawal (nights 29 to 42) in Patients With Primary Insomnia



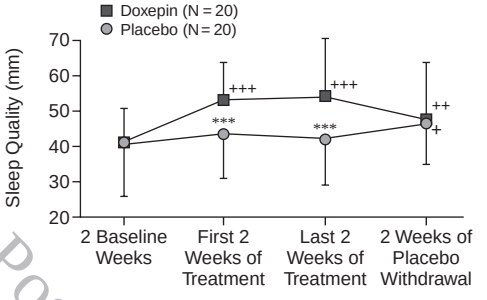
**p < .01, group comparison.
+++p < .001 compared with baseline within the doxepin group.
++p < .01 compared with baseline within the doxepin group.
+p < .05 compared with baseline within the doxepin group.

Figure 5. Wake After Sleep Onset (WASO) After Doxepin and Placebo Administration Over 4 Weeks (nights 1 to 28) and Placebo Withdrawal (nights 29 to 42) in Patients With Primary Insomnia



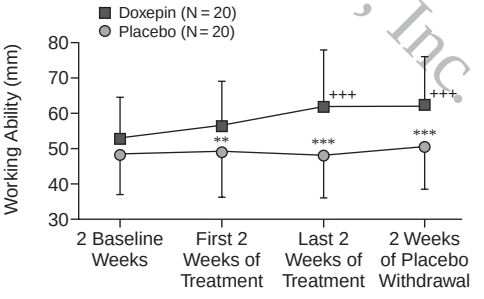
**p < .01, group comparison.
++p < .01 compared with baseline within the doxepin group.

Figure 6. Subjective Sleep Quality Expressed as Mean Values Over 2 Weeks After Doxepin and Placebo Administration Over 4 Weeks (day 1 to 28), and Placebo Withdrawal (day 29 to 42) in Patients With Primary Insomnia[a]



[a]Sleep quality: 0 mm = very poor night, 100 mm = very good night.
***p < .001, group comparison.
+++p < .001 compared with baseline within the doxepin group.
++p < .01 compared with baseline within the doxepin group.
+p < .05 compared with baseline within the placebo group.

Figure 7. Subjective Daytime Working Ability Expressed as Mean Values Over 2 Weeks After Doxepin and Placebo Administration Over 4 Weeks (day 1 to 28) and Placebo Withdrawal (day 29 to 42) in Patients With Primary Insomnia[a]



[a]Working ability: 0 mm = very distracted, 100 mm = very concentrated.
**p < .005, group comparison.
***p < .001, group comparison.
+++p < .001 compared with baseline within the doxepin group.

Rebound

Mean changes from baseline values of all 4 rebound parameters (SE, TST, WASO, sleep stage II percentages) were not significantly affected by acute doxepin withdrawal (nights 29–31) compared with the spontaneous night-to-night variation seen in the placebo group (Table 4). Mean rebound analysis further revealed that SE ($p \leq .10$) and WASO ($p \leq .05$) were more improved after 2 weeks of doxepin withdrawal than during continuous placebo intake (Table 4).

The detailed rebound analysis showed that rebound phenomena in at least 1 rebound item in at least 1 of the acute withdrawal nights were seen in 18 patients (90%) of the doxepin group and 19 patients (95%) of the placebo group. After 2 weeks of withdrawal, there was at least 1 rebound sleep parameter below pretreatment values in 10 patients (50%) of the doxepin group and 11 patients (55%) of the placebo group. Following doxepin treatment, the rebound rate of patients showing rebound in 3 or 4 sleep parameters (TST, SE, WASO, sleep stage II percentages) was increased at all nights of acute withdrawal (night 29, $p \leq .01$; night 30, $p \leq .01$; night 31, $p \leq .05$) compared with continuous placebo application (Table 4). Despite the higher rebound rate after doxepin withdrawal, maximal amounts of worsened sleep in the doxepin group did not exceed those of the placebo group (Table 4). Group comparisons done for each night of withdrawal revealed that the amount of rebound was more expressed for WASO after acute doxepin withdrawal (night 29) ($p \leq .05$) but less expressed for TST ($p \leq .005$) and sleep stage II percentages ($p \leq .05$) after 2 weeks of doxepin withdrawal (Table 4).

Table 4. Mean Changes From Baseline Values After Doxepin Withdrawal (N = 20) or Placebo Discontinuation (N = 20) and Amount of Rebound and Rebound Rate in Those Patients With Primary Insomnia Who Experienced Rebound[a]

	Change From Baseline, Mean ± SD			
Variable	Night 29	Night 30	Night 31	Night 42
TST, min				
Placebo	14.42 ± 50.63	–6.75 ± 59.46	–9.48 ± 51.77	–8.05 ± 65.08
Doxepin	–10.20 ± 50.48	–6.18 ± 49.42	–7.43 ± 69.06	18.63 ± 52.57+
SE, %				
Placebo	3.73 ± 6.42	0.05 ± 9.48	2.10 ± 7.41	1.37 ± 8.23
Doxepin	–0.08 ± 8.56	1.21 ± 11.80	2.92 ± 16.54	7.53 ± 10.94*
WASO, % SPT				
Placebo	–2.13 ± 4.38	–0.17 ± 9.60	–2.39 ± 8.15	–0.75 ± 7.74
Doxepin	–0.25 ± 7.49	–2.96 ± 13.48	–3.85 ± 16.83	–8.47 ± 15.19
Stage II, % SPT				
Placebo	0.13 ± 4.57	–1.59 ± 8.54	–1.13 ± 4.97	–1.02 ± 8.26
Doxepin	–2.59 ± 6.51	–2.46 ± 9.28	–2.89 ± 12.09	3.23 ± 15.19
	Amount of Rebound, Mean ± SD			
	Night 29	Night 30	Night 31	Night 42
TST, min				
Placebo	–42.92 ± 31.77 (N = 6)	–63.63 ± 3.56 (N = 8)	–41.58 ± 39.64 (N = 12)	–77.13 ± 38.96 (N = 8)
Doxepin	–44.50 ± 28.61 (N = 12)	–39.23 ± 30.36 (N = 11)	–52.23 ± 32.79 (N = 11)	–22.39 ± 14.17** (N = 8)
SE, %				
Placebo	–5.30 ± 4.47 (N = 3)	–8.56 ± 5.59 (N = 8)	–4.90 ± 7.05 (N = 7)	–9.20 ± 6.62 (N = 6)
Doxepin	–7.36 ± 5.14 (N=10)	–6.53 ± 5.01 (N = 11)	–9.99 ± 7.23 (N = 9)	–3.20 ± 2.97 (N = 6)
WASO, % SPT				
Placebo	2.16 ± 2.19 (N = 6)	9.63 ± 6.81 (N = 7)	5.82 ± 5.53 (N = 6)	8.20 ± 7.90 (N = 6)
Doxepin	6.70 ± 4.22* (N = 9)	4.71 ± 5.27 (N = 11)	9.98 ± 5.80 (N = 8)	1.72 ± 2.10 (N = 5)
Stage II, % SPT				
Placebo	–3.45 ± 3.04 (N = 8)	–6.04 ± 6.10 (N = 13)	–5.37 ± 3.07 (N = 10)	–10.54 ± 5.06 (N = 7)
Doxepin	–6.82 ± 4.79 (N = 12)	–7.33 ± 4.97 (N = 13)	–10.35 ± 7.34 (N = 12)	–4.80 ± 3.13* (N = 7)
	Rebound Rate (N)			
	Night 29##	Night 30##	Night 31#	Night 42
1 item				
Placebo	5	5	4	2
Doxepin	1	6	3	3
2 items				
Placebo	6	5	3	4
Doxepin	1	0	1	2
3 items				
Placebo	1	0	5	1
Doxepin	5	3	1	3
4 items				
Placebo	4	2	3	3
Doxepin	7	7	9	2

[a]Rebound = deterioration of sleep efficiency, total sleep time, wake after sleep onset, and/or sleep stage II percentages from sleep period time below pretreatment values. Abbreviations: SE = sleep efficiency; Stage II (% SPT) = sleep stage II percentages from sleep period time; TST = total sleep time; WASO = wake after sleep onset.
+$p \leq .1$, compared with placebo.
*$p \leq .05$, compared with placebo.
**$p \leq .01$, compared with placebo.
#$p \leq .05$, chi-square distribution.
##$p \leq .01$, chi-square distribution.

Side Effects

Adverse events occurred in all 24 patients (100%) of the doxepin group and in 21 (91.3%) of the 23 patients of the placebo group. Neither the total number of side effects nor the frequency of particular adverse events differed significantly between the groups. Dry mouth, dizziness, and somnolence tended to be more pronounced in the verum group, while diarrhea, dyspepsia, anorexia, sweating, and common colds were more frequent in the placebo group (Table 5).

DISCUSSION

To our knowledge, this is the first double-blind, placebo-controlled study investigating the effects of antidepressants on polysomnographic recorded sleep in pa-

Table 5. Most Common Side Effects In All Patients as Measured by Fischer Somatic or Undesired Effects Check-List (FSUCL)

	Doxepin (N = 24)		Placebo (N = 23)	
Side Effect	N	%	N	%
Dry mouth	17	70.8	12	52.2
Headache	6	25.0	8	34.8
Constipation	4	16.7	6	26.1
Increased appetite	5	20.8	4	17.4
Hypotonia	4	16.7	5	21.7
Sweating	2	8.3	6	26.1
Dizziness	5	20.8	2	8.7
Common cold	2	8.3	5	21.7
Nervousness	3	12.5	4	17.4
Nausea	2	8.3	4	17.4
Disturbed accommodation	2	8.3	3	13.0
Asthenia	3	12.5	2	8.7
Abnormal dreams	2	8.3	3	13.0
Somnolence	4	16.7	1	4.3
Anorexia	1	4.2	3	13.0
Dyspepsia	1	4.2	3	13.0
Diarrhea	0	0.0	3	13.0
Dysuria	0	0.0	2	8.7
Skin irritation	0	0.0	2	8.7
Exanthema	2	8.3	0	0.0
Abnormal vision	2	8.3	0	0.0
Increased weight	2	8.3	0	0.0

tients with primary insomnia. It is the major finding of this study that even low doses of doxepin of 25 or 50 mg improve sleep in patients with chronic primary insomnia compared with placebo. The effects of acute (first day of treatment) and subchronic (4 weeks) doxepin administration were mainly expressed in significant increases of sleep efficiency (SE). An increase in SE of about 10% and in total sleep time (TST) of about 50 minutes at the first day of treatment indicates a remarkable sleep-promoting power of doxepin even after low-dose single administration. The persistence of the sleep-improving effects after 4 weeks of treatment demonstrate long-term efficacy of doxepin on sleep in insomniacs. Effects of study setting on the efficacy of doxepin could be ruled out, since placebo failed to improve sleep after both acute and subchronic administration.

Changes in global sleep parameters were mainly caused by increases of sleep stage II. Contrary to the well-documented suppressive effects of TCAs on REM sleep, REM sleep latency and REM sleep percentages were not significantly affected by doxepin. Similar results have already been reported in an open pilot study.[34] As a consequence, the nonREM–REM-sleep architecture was preserved. These results agree with reports about less marked REM sleep alterations by doxepin compared with other TCAs,[69] although TCAs (except trimipramine[33,37,47,70,71]) have been generally noticed to delay and deprive REM sleep.[72] The negligible REM suppressive action of doxepin in this study is most probably due to the intake of 25 to 50 mg doxepin, which is far below doses applied for the treatment of major depression. Taken together, the polysomnographic findings of this study confirm sleep-improving effects of TCAs in primary insomnia, which have been reported earlier for doxepin and trimipramine in an open,[34] and single-blind study, respectively.[35] The results also confirm the well-known sleep-improving effects of TCAs in normal subjects and depressed patients.[39–44,46,47,73]

Statistically significant improvements in objective sleep by the TCA doxepin appeared to be of clinical significance for the actively treated group, although doxepin did not abolish all of the patients' sleep problems. Sleep efficiency improved markedly with doxepin, to 89% at the first day of treatment, and remained at this level even after 4 weeks of treatment. However, sleep efficiency levels of greater than 90% to 95% may be suggested as normal in middle-aged humans and were not reached during the treatment. Total sleep time increased by 53 minutes at the first day of treatment compared with baseline and remained improved by 51 minutes at the last day of treatment. Average total sleep time at day 28 of active treatment was as high as 7.1 hours. The treatment failed to normalize each objective sleep parameter as would be expected on the basis of results from all other studies performed to evaluate antidepressants in the treatment of insomnia.[34,35,55,56] For example, wake time after sleep onset after 4 weeks of doxepin treatment was reduced by half from 78.0 minutes at baseline but was still 35.8 minutes. Nevertheless, objective sleep improvement by doxepin was confirmed by subjective ratings given by the patients. Both subjective sleep quality and daytime working ability were significantly increased following doxepin treatment compared with placebo treatment. The objective and subjective sleep improving effects of doxepin were reflected by significant improvements in the items taken from the CGI, which were rated by the investigators. Global improvement was significantly better in the doxepin group than in the placebo group at the first day of treatment.

While many effects of doxepin on sleep were significantly better than those of placebo, the insomniac patients appeared not to be completely satisfied by their treatment. While the mean value of subjective sleep quality during doxepin treatment significantly increased from 41 mm at baseline, it reached only 54 mm in the visual analogue scale, which ranged from 0 mm = very poor night to 100 mm = very good night. Also, working ability increased significantly during treatment and remained improved during withdrawal, but subjective energy remained unaffected. Investigators underlined a light-to-moderate improvement of the patients in this study. Ratings of global improvement in the CGI were significantly better after doxepin than after placebo treatment only at the first day of treatment. Doxepin minimally improved the patients' state, while no change was found in the placebo group. After 4 weeks of treatment, patients were much improved after doxepin and minimally improved after placebo, although this difference was not statistically significant. No

significant differences between the effects of the active drug and placebo were found for severity of illness either. At least both treatment groups improved from markedly to moderately ill to ratings of mildly to moderately ill. Finally, it has to be considered that significant improvements in sleep parameters were restricted in their duration to the period of active treatment. Sleep efficiency returned from 90% to pretreatment values of about 80% after the end of active treatment. Obviously, patients were symptomatically treated, not cured.

Criteria for ideal sleep-promoting agents require sleep-inducing and sleep-maintaining properties. In this study, doxepin did not reduce latency to sleep onset after either acute or subchronic intake. This was due to the fact that most patients showed disturbances in maintaining sleep in their polysomnographic recordings but had sleep latencies within the normal range. Similar problems have come up during single-blind treatment of 15 chronic insomniacs with an average of 166 ± 48 mg of trimipramine.[35] Sleep efficiency, TST, and sleep stage II percentages were improved, but baseline sleep latencies of below 30 minutes were not significantly affected. Unfortunately, the trimipramine study and the present study leave the question open whether TCAs improve sleep onset in patients with insomnia. This may impair the usefulness of doxepin as sleep medication in clinical practice since most insomniacs have been found to complain of problems with both initiating and maintaining sleep.[74]

Besides the hypnotic properties of doxepin, withdrawal and rebound symptoms have to be considered in the evaluation of its benefit/risk ratio as a sleep-promoting agent. An increasing number of reports have described withdrawal effects of TCAs, especially after long-term administration in patients with depression.[50–54] Since sleep disturbances are one of the most prominent withdrawal symptoms of sedating TCAs in depressed patients, it is likely that abrupt discontinuation of doxepin may cause withdrawal symptoms in insomniac patients. In the present study, the unchanged values of daytime energy as well as the persistence of an improved working ability indicated no subjective withdrawal effects. In contrast to withdrawal, rebound insomnia has been defined as a worsening of one or more sleep parameters below pretreatment levels after discontinuation of the drug intake.[63–65] Doxepin did not cause rebound insomnia when rebound in polysomnographic sleep parameters was analyzed according to standard methods. Changes in mean values of sleep parameters before and after treatment were not significantly different between treatment groups. Very similar to these results, no rebound insomnia was reported for insomniac patients withdrawn from trimipramine treatment.[35] Since mean changes from baseline values often failed to reflect the occurrence of rebound insomnia,[66] we also calculated the number of patients with rebound (i.e., the rebound rate) for those sleep parameters that showed significant effects during the treatment period. We found that neither the rebound rate for at least 1 of the rebound sleep parameters nor the amount of rebound (in the patients having rebound) differed significantly between the treatment groups. However, some doxepin patients were more likely to experience severe rebound insomnia than placebo patients. The number of doxepin-treated patients showing rebound in 3 or more rebound sleep parameters during the acute withdrawal period was significantly greater than in the placebo group. We conclude from our data and the literature that withdrawal effects may appear in some insomniac patients even after subchronic (4 weeks) treatment. Thus, rebound insomnia should be taken into account when TCAs are used for the treatment of insomnia. Abrupt discontinuation of TCAs should be avoided, while tapered discontinuation is recommended.

Besides withdrawal and rebound symptoms, side effects limit the use of doxepin as a sleep-promoting agent in general practice. TCAs may induce neural symptoms and sedation, impairment of memory and appetite, and alterations in blood counts and ECG.[75,76] In fact, in this study, 2 of 4 doxepin-treated patients who dropped out had severe side effects like leukopenia, thrombopenia, and increased liver enzymes. The remaining patients did not show side effects that were statistically different from the placebo group, while the total number of patients with side effects was high in both treatment groups. Neither the total number of side effects nor the occurrence of specific adverse events was increased after doxepin intake compared with placebo. We suggest that the sleep-inducing properties of doxepin have to be carefully weighted against possible side effects and that analysis of blood count and liver enzymes as well as ECGs must be performed regularly to control for severe and dangerous adverse events.

In summary, our polysomnographic data underline the hypnotic efficacy of doxepin in primary insomnia even after 4 weeks of treatment with clear advantage in improving sleep maintenance. Objective sleep-improving effects were paralleled by slight-to-moderate improvements in subjective ratings of both the patients and the investigators. Physicians prescribing doxepin to insomniacs are required to pay attention to its specific side effects and to avoid abrupt discontinuation of drug intake to prevent the occurrence of rebound insomnia. We conclude that doxepin is a reasonable alternative for the treatment of insomniacs who cannot be treated by benzodiazepine receptor agonists (e.g., chronic insomniacs with a history of drug dependency or the need for long-term treatment). Since treatment duration in this study was restricted to 4 weeks, long-term benefits will have to be determined in future studies.

Drug names: amitriptyline (Elavil and others), doxepin (Sinequan and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), trazodone (Desyrel and others), trimipramine (Surmontil).

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