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A Double-Blind, Randomized, Parallel-Group, Prospective Clinical Study for Evaluation of Efficacy and Safety of Doxepin in Comparison with Zopiclone in Patients with Primary Insomnia

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ABSTRACT

Background: Aim: Doxepin is a tricyclic antidepressant with sedative properties at low doses. Its advantage is that it has no dependence potential unlike the conventional hypnotics. This study aims to evaluate the safety and efficacy of Doxepin with one of the conventional hypnotic Zopiclone in the treatment of primary insomnia. **Methods:** This is a prospective, interventional, double-blind, randomized, parallel-group (two arms) study conducted at a private psychiatry clinic in Central India as a part of multi-centre clinical trial. A total of 21 patients with Primary insomnia defined as per DSM-IV TR (having mean subjective latency of sleep onset (LSO) ≥ 20 minutes, wake-time after sleep onset (WASO) ≥ 60 minutes and total sleep time (TST) ≤ 390 minutes) were screened at our site in a placebo run-in period of 3 days and out of them 20 patients fulfilling the selection criteria were enrolled in the study. Then they were randomized to either Doxepin or Zopiclone (10 patients on Doxepin and 10 patients on Zopiclone). These patients were followed up prospectively on Day 8th and Day 14th after randomization and the efficacy of these two drugs was compared on wake-time after sleep onset (WASO), subjective latency of sleep onset (LSO), total sleep time (TST) and sleep efficiency (SE) which were assessed in these follow up visits. Tolerability to the study drugs were assessed by evaluation of adverse events reported voluntarily, observed on physical and systemic examination, or found on laboratory investigations during the study period. **Results:** Patients from both of the treatment groups (Doxepin and Zopiclone) responded well to respective drugs. Doxepin 3 mg was found to be equally effective in terms of improvement in various efficacy parameters like WASO, LSO, TST and SE compared to Zopiclone (statistically significant improvement in both the groups:- Doxepin: $p=0.003$; Zopiclone: $p<0.001$). Similarly, both the treatments were well tolerated as evidenced by similar changes in mood and alertness on final wakening. Also, in terms of safety, there were no reported serious adverse events with Doxepin. **Conclusion:** Low dose Doxepin can be an important effective therapeutic option in the treatment of insomnia without having the risk of dependence. However, considering the small sample size from this center, it is suggested that the data/results presented in this report should be read in conjunction with the data from other centers.

Keywords: Doxepin, Zopiclone, Primary insomnia.

INTRODUCTION

Insomnia consists of a complaint of disturbed sleep, which presents as difficulty in sleep initiation or maintenance, and/or early awakenings. Insomnia also includes the presence of daytime impairments to normal functioning as a result of sleep insufficiency. These impairments are generally manifested as fatigue, irritability, a decrease in memory and concentration, and malaise.[1,2]

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According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for primary insomnia requires: (i) a predominant complaint of difficulty in initiating or maintaining sleep, or non-restorative sleep, for at least 1 month; (ii) that the sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; (iii) that the sleep disturbance does not occur exclusively during the course of another sleep disorder (e.g., narcolepsy, breathing-related sleep disorder, etc.); and (iv) that the disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another psychiatric or general medical condition.

In recent years, insomnia treatment has advanced beyond the routine use of benzodiazepines and benzodiazepine like drugs. Newer drug options are less likely to cause tolerance, dependence, and withdrawal. Doxepin is one such drug for the treatment of insomnia.

Doxepin have several distinctive advantages over other available hypnotic agents for several reasons. First, it is a non-controlled substance that enjoys virtually no risk of addiction or dependence. This allows easier prescribing with fewer prescribing restrictions, as well as being potentially effective in high-risk patient populations (e.g., history of alcohol or drug abuse) and those who require a pharmacologic agent on a more chronic basis. Second, it is has good-quality, placebo-controlled data for use in the elderly, and current data support its safe use even at the highest tested dose of 6 mg. Side effects even at the 6-mg dose seemed favorable compared with placebo. Therefore, low dose doxepin is expected to be an important treatment option for patients with primary insomnia.[3-5]

Need of current study

The most commonly used pharmacologic agents approved for the treatment of insomnia include zolpidem, temazepam and eszopiclone. This class of agents has been associated with side-effects such as daytime sedation, motor incoordination, cognitive impairment, and related concerns about increases in the risk of motor vehicle accidents and injuries from falls6. These agents have also been associated with the potential for abuse and dependence in at-risk populations, which led the U.S. Drug Enforcement Agency to classify them as Schedule IV substances7. For the treatment of insomnia, sedating antidepressants such as trazodone are commonly used off-label in clinical practice. However, the limited available data on the use of these agents indicate that when used for insomnia at antidepressant doses they are associated with undesirable side-effects. Additionally, the efficacy, safety and optimal dosages of these drugs have not been systematically defined.

Doxepin, a compound with potent histamine blocking activity (mainly H1), has long been known to have significant sleep promoting effects8. Similar to the other commonly prescribed compounds used off-label to treat insomnia, doxepin at doses ≥25 mg is associated with undesirable side effects, including significant anticholinergic effects9. Additionally, when used at these higher doses, the selectivity of doxepin for H1 receptors is compromised because the other less selective receptor systems take on additional physiological importance.

Oral doxepin 3 mg and 6 mg has been approved in the US for the treatment of insomnia characterized by difficulty in maintaining sleep. In phase III trials in adult and elderly patients with chronic primary insomnia, oral, low-dose doxepin was more effective than placebo at reducing the signs and symptoms of primary insomnia. Low-dose doxepin significantly improved wake-time after sleep onset (WASO), total sleep time (TST) and sleep efficiency (SE) compared with placebo and the improvements seen on the first night were maintained over 1–3 months. Low-dose doxepin was generally well tolerated, with the most common adverse event being somnolence/ sedation.[10,11]

Doxepin is not yet approved in India specifically for treating insomnia. A number of published reports indicated that low-dose doxepin was safe and effective in the treatment of primary insomnia in the adult and elderly patients.

With this backdrop, the current study was planned to evaluate the safety and efficacy of doxepin 3 mg tablet in comparison with zopiclone 3.75 mg for the treatment of primary insomnia in Indian patients.

Aim Of The Study

The objective of the study was to evaluate the safety and efficacy of Doxepin 3 mg oral tablet formulation versus Zopiclone 3.75 mg tablet in the treatment of primary insomnia.

MATERIALS AND METHODS

Study Design

The study was a part of double-blind, randomized, parallel-group (two arms), active-controlled, prospective, multi-centre clinical study. The data presented here is from our centre only. All patients provided written informed consent prior to the start of study.

Sample Size

At this centre, 20 patients meeting selection criteria were enrolled.

Patient Population

Inclusion criteria

- Patients (either sex & 18 to 75 years of age) of primary insomnia as defined by DSM-IV TR for at least one month were screened for this study.
- Patients having mean subjective latency of sleep onset (LSO) ≥ 20 minutes, WASO ≥ 60 minutes and TST ≤ 390 minutes during placebo run-in period were selected for the study.

  In case of female patients of childbearing potential: non-pregnant, non-lactating with negative serum pregnancy test at screening were willing to utilize an acceptable method of contraception throughout the study period

Exclusion criteria

- Patients with a history of sleep apnea syndrome.
- Concomitant history of cognitive disorders, depression, schizophrenia, panic disorder, dementia, chronic pain, glaucoma, frequent nightly urination; significant hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, hematological,

metabolic disorders; history of suicidal tendency, fibromyalgia, seizures (excluding childhood febrile seizures), and chronic obstructive pulmonary disease.

- Known hypersensitivity to any of study medications, participation in any other investigational study and/or taken any investigational drug within 30 days prior to the enrolment date, requirement or intention to continue taking any disallowed medication or any prescription medication or over-the counter medication that is known to affect the sleep/wake function or otherwise interfere with evaluation of the study medication, use of any CNS medication or other drugs or supplements within 1 week prior to the enrolment that is known to affect sleep pattern, history of drug induced leucopenia/neutropenia/agranulocytosis, serious hepatic disease (SGPT/OT≥2.5 times UNL), Cardiac arrhythmia, QT prolongation or conditions predisposing for prolongation of QT interval, hyperglycemia (random blood sugar ≥ 140 mg/dl) or diabetes mellitus, any other clinically important abnormal finding, requirement of sleep schedule changes as a part of professional duty.
- History of substance abuse including tobacco, alcohol and caffeine or as deemed inappropriate for enrollment by investigating physician due to other reasons.

Visits and Treatment Plan

Adult patients (18-75 years of age) suffering from primary insomnia for the last one month were considered eligible for screening and subsequently for enrollment. At the screening visit (i.e., visit 1), patients were supplied placebo tablets for 3 days (as one tablet daily 30 minutes prior to the bedtime.

After screening, patients who fulfilled all the selection criteria were randomized (on visit 2, i.e., day 1) to receive one tablet of either Doxepin 3 mg or Zopiclone 3.75 mg 30 minutes before the bedtime for initial 7 days. On visit 3 (Day 8±2), dose of study drugs was doubled to two tablets daily in patients who had not achieved significant improvement in insomnia (i.e., ≥ 50% reduction in WASO). The dosage decided on visit 3 was continued through 14th day. At the end of the study (i.e., visit 4), patients were changed over to commercially available treatment option as per discretion of the investigator.

During the study, if the patient was not able to tolerate the dose or demonstrating intolerable side effects, he was dropped out from the study if the investigator deems so in the best interest of the patient and was treated according to the investigator's discretion.

Evaluation Criteria

Efficacy parameters

- Both treatment groups were compared for the following efficacy parameters:

Primary efficacy parameter:

- Change in the WASO at the end-of-study compared to baseline.

Secondary efficacy parameters:

- Change in latency to sleep onset (LSO) at the end of treatment compared to baseline.
- Change in total sleep time (TST) at the end of treatment compared to baseline.
- Change in sleep efficiency (SE) at the end of treatment compared to baseline.

Safety parameters

- Safety was evaluated in both treatment groups based on the following criteria:
- Change in alertness and mood on final wakening (recorded as VAS) at the end of treatment compared to baseline.
- Change in Epworth sleepiness scale score at the end of treatment compared to baseline.
- Any adverse event reported voluntarily, observed or enquired during the study period.
- Any clinically significant change in laboratory investigation values, vital signs, and physical examination during the study were compared with the baseline. However, minor deviations in laboratory results from the baseline were allowed without a need to report them as adverse drug reactions if they were without clinical symptoms.

Statistical Analysis

Results were expressed as mean ± standard deviation. Statistical analysis was performed on intention-to-treat data set and data from all patients who completed assessments at least up to follow-up 1 (considered evaluable for study drug efficacy and safety) were included for analysis as the 'last observation carried forward (LOCF)' data. To determine the level of significance of the observed difference of values in the two treatment groups, Student's 't' test was applied to all quantitative parametric data and Chi-square or Mann-Whitney test to nonparametric data. Statistical significance was fixed at 5% level (95% confidence interval; $P < 0.05$).

RESULTS

A total of 21 patients were screened and out of that 20 patients (10 on doxepin and 10 on zopiclone treatment) were enrolled at this trial site. Baselines characteristics with respect to age, body weight, height & and other sleep parameters were matching in both treatment groups. [Table 1] Dose of study medication was doubled (2 tablets) on 8th day in 3 patients from doxepin group and 1 patient from zopiclone group and the same dose continued

through study end. None of the patients had hypertension, diabetes mellitus, thyroid disorder and none were on any concomitant medications at the start of study drug therapy.

Table 1: Baseline characteristics of patients.

Parameter	Doxepin (N = 10)	Zopiclone (N = 10)
Age (Years) (Mean ± SD)	49.30±13.38	43.20±11.32
Sex ratio (Female: Male)	5:5	6:4
Body weight (kg) (Mean ± SD)	58.40±10.46	55.50±9.76
Height (cm) (Mean ± SD)	164.40±5.15	160.90±4.23
No. of Pts with complaint of sleep initiation	10	10
No. of Pts with complaint of sleep maintenance	10	10
Duration of complaint (months)(Mean ± SD)	3.80±3.36	4.0±2.45
Baseline WASO (min) (Mean ± SD)	152.17±53.61	131.83±55.64
Baseline LSO (min) (Mean ± SD)	91.0±27.45	93.83±30.53
Baseline TST (min) (Mean ± SD)	193.83±47.19	242.33±87.24

Both the treatments were found to be equally effective in terms of improvement in efficacy parameters like WASO. Both the doxepin and zopiclone showed significant improvement (P=0.003 and P<0.001 respectively) in the efficacy parameters at study end compared to those values at baseline. [Table 2].

Both the study drugs showed significant improvement (P < 0.05) in the efficacy parameters like LSO at study end compared to those values at baseline. [Table 3].

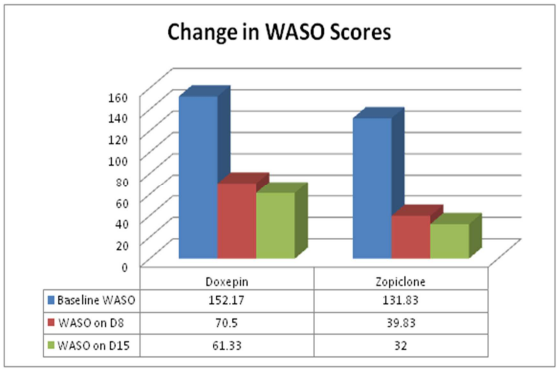

Figure 1: Comparison of WASO scores in both the groups.

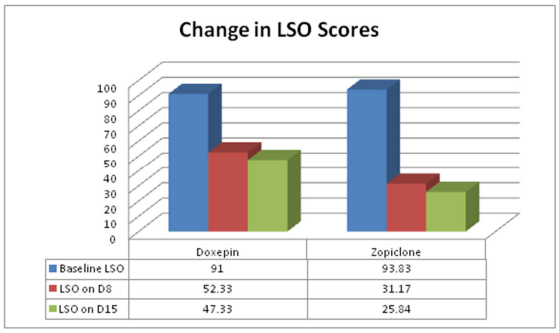

Figure 2 : Comparison Of LSO scores in Both the Groups.

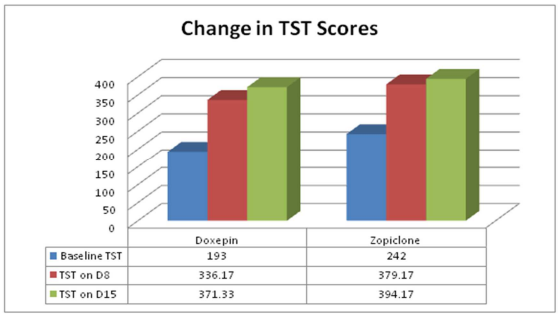

Figure 3: Comparison of Both the groups in TST scores.

Table 2: Change in WASO at the end of study treatment compared to baseline.

	WASO at Baseline	WASO on day 8		WASO on day 15		P value: Day 15 Vs Baseline
Treatment Group	**Value (min)**	**Value (min)**	**% change**	**Value (min)**	**% change**	
Doxepin (N = 10)	152.17±53.61	70.50±67.64	53.67	61.33±69.92	59.69	0.003
Zopiclone (N = 10)	131.83±55.64	39.83±42.09	69.79	32.0±35.53	75.73	<0.001
P value: Doxepin vs Zopiclone	0.416	0.239		0.252		

Table 3: Change in LSO at the end of study treatment compared to baseline.

	LSO at Baseline	LSO on day 8		LSO on day 15		P value: Day 15 Vs Baseline
Treatment Group	**Value (min)**	**Value (min)**	**% change**	**Value (min)**	**% change**	
Doxepin (N =10)	91.0±27.45	52.33±39.93	42.49	47.33±35.43	47.99	<0.001
Zopiclone (N = 10)	93.83±30.53	31.17±29.94	66.78	25.84±23.55	72.46	<0.001

P value: Doxepin vs Zopiclone	0.830	0.172		0.127		

Table 4: Change in TST at the end of study treatment compared to baseline.

	TST at Baseline	TST on day 8		TST on day 15		P value: Day 15 Vs Baseline
Treatment Group	**Value (min)**	**Value (min)**	**% change**	**Value (min)**	**% change**	
Doxepin (N =10)	193.83±47.19	336.17±90.95	-73.44	371.33±100.94	-91.58	<0.001
Zopiclone (N =10)	242.33±87.24	379.83±69.91	-56.74	394.17±68.15	-62.66	<0.001
P value: Doxepin vs Zopiclone	0.139	0.244		0.561		

Table 5: Change in SE at the end of study Treatment compared to baseline.

	SE at Baseline	SE on day 8		SE on day 15		P value: Day 15 Vs Baseline
Treatment Group	**Value (%)**	**Value (%)**	**% change**	**Value (%)**	**% change**	
Doxepin (N =10)	44.52±10.74	73.49±19.70	-65.07	77.22±19.33	-73.45	<0.001
Zopiclone (N = 10)	50.86±13.44	84.03±15.11	-65.22	87.04±13.48	-71.14	<0.001
P value: Doxepin vs Zopiclone	0.259	0.196		0.204		

Table 6: Change in Sleep Quality at the end of study treatment compared to baseline.

	Sleep Quality at Baseline	Sleep Quality on day 8		Sleep Quality on day 15		P value: Day 15 Vs Baseline
Treatment Group	**Value (%)**	**Value (%)**	**% change**	**Value (%)**	**% change**	
Doxepin (N = 10)	18.40±4.71	35.77±8.38	-94.40	38.60±8.86	-109.78	<0.001
Zopiclone (N =10)	17.83±7.014	36.44±10.04	-104.37	38.33±10.77	-114.97	<0.001
P value: Doxepin vs Zopiclone	0.835	0.874		0.952		

Table 7: Change in Mood of final wakening at the end of study treatment compared to baseline.

	Baseline	On day 8		On day 15		P value: Day 15 Vs Baseline
Treatment Group	**Value (%)**	**Value (%)**	**% change**	**Value (%)**	**% change**	
Doxepin (N =10)	18.47±5.29	36.50±7.93	-97.62	38.53±8.51	-108.61	<0.001
Zopiclone (N = 10)	18.53±7.4	37.20±10.55	-100.76	38.13±10.60	-105.77	<0.001
P value: Doxepin vs Zopiclone	0.981	0.869		0.927		

Table 8: Change in Alertness on final wakening at the end of study treatment compared to baseline.

	Baseline	On day 8		On day 15		P value: Day 15 Vs Baseline
Treatment Group	**Value (%)**	**Value (%)**	**% change**	**Value (%)**	**% change**	
Doxepin (N =10)	18.30±4.70	36.57±7.81	-99.84	38.70±8.46	-111.48	<0.001
Zopiclone (N =10)	19.07±7.08	37.03±10.60	-94.18	38.87±11.23	-103.83	<0.001
P value: Doxepin vs Zopiclone	0.779	0.912		0.970		

In terms of sleep duration, TST and overall SE were statistically significantly increased in both the treatment group ($P < 0.05$) at study end compared to those values at baseline. [Tables 4 & 5].

Both the treatments were well tolerated as evidenced by similar changes in sleep quality, mood and alertness of final wakening in both the treatment groups at treatment end compared to baseline values [Tables 6, 7, 8].

At baseline all patients showed normal ESS score. (i.e. between 0 to 9), represented no day time sleepiness. After 2 weeks of treatment, both study drugs showed no significant change in ESS score

and also there was no significant difference observed between the study treatment groups.

Laboratory Parameters:

Mean values of hematology and biochemistry investigation results at screening and end-of-study for two treatment groups are shown in [Table 9]. Results of this analysis did not reveal clinically significant deviation of values of any of the parameters. [Tables 9]

Table 9: Laboratory investigation values at baseline and at study end in the two treatment groups

Parameters	Values (Mean ± S.D.)			
	Doxepin (N=10)		Zopiclone (N=10)	
	Screening	End of Study	Screening	End of Study
Hemoglobin (g/dl)	12.93±1.42	13.26±1.39*	12.27±2.32	12.36±2.03
RBC (million cells/mm3)	4.79±0.55	4.79±0.44	4.77±0.63	4.71±0.60
WBC (cells/mm3)	8590.0±1724.63	7490.0±879.96*	8020.0±2148.80	8290.0±1254.72
(WBC differential count)				
Neutrophils (%)	65.60±4.50	66.50±3.34	57.10±2.88	63.40±2.91*
Lymphocytes (%)	30.80±4.98	30.50±3.63	35.90±8.31	33.10±3.57
Eosinophils (%)	1.50±0.97	1.40±0.52	2.90±2.08	1.80±1.23*
Monocytes (%)	1.90±0.88	1.60±0.52	2.20±1.75	1.70±1.25
Basophils (%)	0.0±0.0	0.00±0.0	0.0±0.0	0.0±0.0
Platelet (lakh/mm3)	2.54±0.51	2.79±0.45*	2.89±0.75	3.08±0.67*
S. Urea (mg/dl)	22.62±9.44	24.10±7.08*	21.48±8.32	23.87±4.77
S. Creatinine (mg/dl)	0.89±0.5	0.91±0.08	0.84±0.10	0.87±0.10
SGOT (U/ml)	17.10±2.42	24.0±4.71*	23.60±6.06	26.10±4.95
SGPT (U/ml)	20.0±3.50	27.60±3.75*	27.40±10.34	26.30±7.73
S. Alkaline Phos.(U/ml)	176.0±21.76	168.0±16.30	157.50±25.46	154.70±23.44
S. Bilirubin (mg/dl)	0.69±0.08	0.69±0.12	0.68±0.11	0.69±0.09
Random Blood Sugar (mg/dl)	103.40±18.01	111.30±13.40	108.40±15.76	106.70±15.92

Electrocardiogram (ECG):

Findings of the ECG of all patients were reported as within normal limits both at baseline and study end and did not indicate any significant deviation in either treatment group.

Blood pressure and heart rate:

There was no clinically significant variation observed in both parameters during the study in both treatment groups.

Adverse events reported:

None of the patients in either treatment groups reported any adverse event (AEs) during the treatment period. No serious adverse event was reported in the study.

DISCUSSION

Patients from both of the treatment groups responded well to respective drugs. Doxepin 3 mg was found to be equally effective in terms of improvement in various efficacy parameters like WASO, LSO, TST, and SE compared to zopiclone. Similar results were reported by studies conducted by Krystal AD et al Wu J et al.[12,13]

Krystal AD et al,[12] conducted a study of 159 patients with primary insomnia to evaluate the efficacy and safety of doxepin in elderly subjects with chronic primary insomnia. The study was a randomized, double-blind, parallel-group, placebo-controlled trial. Subjects meeting DSM-IV-TR criteria for primary insomnia were randomized to 12 weeks of nightly treatment with doxepin (DXP) 1 mg (n = 77) or 3 mg (n = 82), or placebo (PBO; n = 81). Efficacy was assessed using polysomnography (PSG), patient reports, and clinician ratings. The study found that DXP 3 mg led to significant improvement versus PBO on N1 in wake time after sleep onset (WASO; P < 0.0001; primary endpoint), total sleep time (TST; P < 0.0001), overall sleep efficiency (SE; P < 0.0001), SE in the last quarter of the night (P < 0.0001), and SE in Hour 8 (P < 0.0001). These improvements were sustained at N85 for all variables, with significance maintained for WASO, TST, overall SE, and SE in the last quarter of the night. DXP 3 mg significantly improved patient-reported latency to sleep onset (Weeks 1, 4, and 12), subjective TST (Weeks 1, 4, and 12), and sleep quality (Weeks 1, 4, and 12). Several global outcome-related variables were significantly improved, including the severity and improvement items of the CGI (Weeks 2, 4, and 12), and all 5 items of the PGI (Week 12; 4 items after Weeks 2 and 4). On the basis of these findings the authors concluded that Doxepin causes chronic significant and sustained improvements in most treatment endpoints in elderly patients with insomnia.

Wu J et al,[13] conducted a study to comprehensively evaluate the dose, treatment duration, treatment efficacy and safety of clinical citalopram and doxepin application in patients with comorbid insomnia and anxiety disorders. It was found that both citalopram (20 mg/day) and low-dose doxepin (12.5 mg/day) significantly improved sleep latency, duration and disturbances, as well as daytime dysfunction and the global Pittsburgh Sleep Quality

Index during the 12-week treatment period. Notably, low-dose doxepin significantly improved sleep latency in patients after treatment for 8 and 12 weeks as compared with citalopram. It was further observed that both citalopram and low-dose doxepin improved anxiety. A significant and positive correlation was found between the improvement in the sleep quality and anxiety in the two treatment groups. The authors concluded that citalopram and low-dose doxepin both showed good efficacy and a low adverse reaction rate in the treated patients.

In this study the treatments were well tolerated as evidenced by similar changes in mood and alertness on final wakening. . In terms of safety, there were no reported adverse event, there were no significant hangover/next-day residual effects with study medications and sleep quality was preserved.

Hajak G et al,[14] conducted a study 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. In this study 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. 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 < or = .001) and subchronic (night 28, p < or = .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 < or = .05) better global improvement at the first day of treatment. Patients rated sleep quality (p < or = .001) and working ability (p < or = .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 < .01, night 30, p < or = .01; night 31, p < or = .05). No significant group differences in side effects were found. On the basis of these findings the authors use of low dose doxepin to improve sleep and working ability in chronic primary insomniacs.

Another study by Roth T et al,[15] conducted a study to evaluate the efficacy and safety of doxepin 1, 3, and 6 mg in insomnia patients. Adults (18-64 y) with chronic primary insomnia (DSM-IV) were randomly assigned to one of four sequences of 1 mg, 3 mg, and 6 mg of doxepin, and placebo in a crossover study. Treatment periods consisted of 2 polysomnographic assessment nights with a 5-day or 12-day drug-free interval between periods. Efficacy was assessed using polysomnography (PSG) and patient-reported measures. Safety analyses included measures of residual sedation and adverse events. The study concluded that in adults with primary insomnia, doxepin 1 mg, 3 mg, and 6 mg was well-tolerated and produced improvement in objective and subjective sleep maintenance and duration endpoints that persisted into the final hour of the night. The side-effect profile was comparable to placebo, with no reported anticholinergic effects, no memory impairment, and no significant hangover/next-day residual effects. These data demonstrate that doxepin 1 mg, 3 mg, and 6 mg is efficacious in improving the sleep of patients with chronic primary insomnia.

CONCLUSION

The results of the study showed that low-dose doxepin can be an effective and safe therapeutic option for the treatment of insomnia. As sample size form this center is very small, the data/results presented in this report should be read in conjunction with the data from other centers.

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