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Original Research Article

Safety and efficacy of ZOLSOMA tablets in patients with insomnia

Sagar Karia[1], Manushree Gupta[2], Manjiri Dikshit[3], Chytanya Deepak[4], Nilesh Shah[1], Pankaj Verma[2], Vidyadhar G. Watve[3], K. Chandra Shekhar[4], Sindhu Amme[5]*, Harsh Chaturvedi[5]

[1]Department of Psychiatry, LTM Medical College and General Hospital, Sion, Mumbai, Maharashtra, India
[2]Department of Psychiatry, VMMC and Safdarjung Hospital, New Delhi, India
[3]Department of Psychiatry, Poona Hospital, Pune, Maharashtra, India
[4]Department of Psychiatry, Asha Hospital and Research Centre, Banjara Hill, Hyderabad, India
[5]Department of Medical Affairs, Pulse Pharmaceuticals Pvt. Ltd., Hitech City, Hyderabad, India

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***Correspondence:**
Dr. Sindhu Amme,
E-mail: medicalaffairs1@pulsepharma.net

ABSTRACT

Background: Insomnia is difficulty falling asleep or staying asleep, even when a person has the chance to do so. Pharmacological management often relies on hypnotics such as zolpidem; however, high doses are linked to adverse effects. Combining zolpidem with melatonin, a circadian regulator with mild hypnotic activity, may enhance sleep quality while minimizing side effects. Aim of the study was to evaluate the safety and efficacy of a fixed-dose combination (FDC) of zolpidem and melatonin (ZOLSOMA-5) in patients with insomnia.
Methods: This open-label, single-arm, multicentre, prospective study was conducted between October 2021 and October 2024. Participants received ZOLSOMA-5 for 30 days. Efficacy was assessed using the Pittsburgh Sleep Quality Index (PSQI), and Insomnia Severity Index (ISI). Safety was evaluated using Epworth Sleepiness Scale (ESS) and based on adverse effects.
Results: Of 312 enrolled patients, 300 completed the study. Mean PSQI scores in intention-to-treat (ITT) set significantly decreased from 15.19±2.75 at baseline to 5.73±5.58 on day 30 ($p<0.001$). ISI scores reduced from 20.57±5.00 at baseline to 7.18±5.45 on day 30, respectively ($p<0.001$). ESS scores improved from 6.99±6.68 at baseline to 4.48±4.70 on day 30 ($p<0.001$). A total of 45 patients (14.4%) reported 60 adverse events (AEs), most commonly dizziness and nausea, the majority were mild and transient.
Conclusions: The FDC of ZOLSOMA-5 demonstrated significant improvement in sleep quality, reducing insomnia severity, and alleviating daytime sleepiness, with a favourable safety profile. The combination appears to be a safe and effective short-term therapeutic option for insomnia, including in patients with psychiatric comorbidities.

Keywords: Insomnia, Zolsoma, Zolpidem, Melatonin, Sleep disorders

INTRODUCTION

Insomnia is the common sleep disorder in adults. Global studies estimate its prevalence to be between 10-35% of the population, some even as high as 50% to 60%. The condition occurs more frequently in older adults, women, and individuals with underlying medical or psychiatric conditions.[1,2]

The condition is characterized by difficulty in initiating or maintaining sleep, which in turn, produces clinically significant distress or impairment in social, occupational, and other important areas of functioning. While some symptoms of insomnia, such as the latency to sleep onset and the frequency and duration of awakenings during the night, can be measured objectively using polysomnography, other symptoms (e.g., daytime fatigue and functional impairment) can only be assessed using

patient reports, and loss of daytime functioning and well-being are considered by patients to be the most serious consequences of insomnia.[3] People with insomnia can feel dissatisfied with their symptoms including sleep onset and maintaining difficulties, satisfaction with sleep, impact on daily functioning and related distress, sleep duration, disturbance, latency, daytime dysfunction efficiency, overall quality, daytime sleepiness and use of sleep medication.

Pharmacologic management of insomnia typically involves hypnotic benzodiazepines (BZD), non-BZD sedatives (Z-drugs), and melatonin receptor agonists.[4]

Melatonin, a biogenic amine secreted by the pineal gland, plays a key role in regulating the sleep–wake cycle. Its secretion increases in darkness and decreases with light exposure, promoting sleep by inducing drowsiness and lowering the body temperature.[5] Melatonin exerts its effects primarily through MT1 and MT2 G-protein coupled receptors, which facilitate sleep onset and synchronize circadian rhythms.[6,7] Unlike conventional hypnotics, melatonin does not induce dependence and is widely used for conditions such as insomnia, circadian rhythm disorders, jet lag, and shift-work-related sleep disturbances.[8]

Subunit modulation of the $GABA_A$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant drug properties. The major modulatory site of the $GABA_A$ receptor complex is located on its alpha (α) subunit and is referred to as the BZD or omega (ω) receptor. At least three subtypes of the (ω) receptor have been identified. Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to BZDs, barbiturates, pyrrolopyrazines, pyrazolopyrimidines or other drugs with known hypnotic properties. It interacts with a GABA-BZD receptor complex and shares some of the pharmacological properties of the BZDs. In contrast to the BZDs, which non-selectively bind to and activate all BZD receptor subtypes, zolpidem *in vitro* binds the (BZD1) receptor preferentially with a high affinity ratio of the alpha1/ alpha5 subunits. The (BZD1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the (BZD1) receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.[9]

Combination products, also known as FDCs, are combinations of two or more active drugs in a single dosage form. Fixed ratio combination products are acceptable when the dosage of each ingredient has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance. The rationality of FDCs makes use of certain aspects including (i) the drugs in the combination should act by different mechanisms; (ii) the pharmacokinetics must not be widely different; and (iii) the combination should not have supra-additive toxicity of the ingredients.[10]

Despite advances in sleep pharmacotherapy, the need remains for agents that enhance restorative sleep without impairing cognitive performance. Combining melatonin with low-dose zolpidem may offer synergistic benefits-enhancing sleep onset and maintenance while reducing adverse effects associated with higher zolpidem doses. Therefore, the present study aims to evaluate the safety and efficacy of ZOLSOMA-5 tablets, a FDC of ZOLSOMA-5, in patients with insomnia.

METHODS

This was a prospective, multicentre, open-label, single-arm, post-marketing study. The study received ethics committee approval, was prospectively registered (CTRI/2021/10/037106), and conducted according to GCP guidelines and the Declaration of Helsinki (2013). Written informed consent was obtained from all participants.

Patients were recruited from four different geographic locations across India through the Departments of Psychiatry at Asha Hospital, Hyderabad; LTM Medical College and General Hospital, Sion, Mumbai; Poona Hospital, Pune; and VMMC and Safdarjung Hospital, New Delhi. Participants included male and female subjects aged 18 years or older with co-morbid disorders, history of daytime complaints associated with disturbed sleep.

Subjects who had consumed any sedative (BZD or barbiturate) within one week, subjects with a history of substance abuse except nicotine use, subjects with known hypersensitivity or any contraindications to the use of any study medication, subjects with chronic illness that might have interfered with trial completion or conduct, and pregnant women, lactating mothers, and women intending pregnancy were excluded from the study.

A total of 335 patients were screened between October 2021 and October 2024, of which 312 were enrolled and 300 completed the study. A minimum sample size of 307 patients was calculated using SAS 9.2 to detect a meaningful change with 90% power and $\alpha=0.05$ using a paired t test.

Eligible subjects received the FDC of Zolpidem Tartrate 5 mg + Melatonin 3 mg [ZOLSOMA-Pulse Pharmaceuticals Pvt. Ltd., Hyderabad, Telangana] orally at night, 30 minutes before bedtime for 30 days. Medical history was recorded at screening and concomitant medications were documented at every study visit. An Adverse drug reaction recording chart was provided to all patients and was reviewed regularly. Follow-up evaluation was done at day 7 and day 30.

The ESS is a self-administered questionnaire that assesses an individual's general level of daytime sleepiness by rating the likelihood of dozing off in eight common daily situations. The total score ranges from 0 to 24, with values of 0-10 indicating normal sleepiness, 11-14 mild sleepiness, 15-17 moderate sleepiness, and 18-24 severe sleepiness.[11]

The ISI is a 7-item self-report scale assessing the severity of insomnia symptoms, including sleep onset and maintenance difficulties, satisfaction with sleep, impact on daily functioning, and related distress. Each item is rated from 0 to 4, giving a total score of 0-28, categorized as 0-7: no significant insomnia; 8-14: sub threshold; 15-21: moderate; and 22-28: severe insomnia.[2]

The PSQI is a 19-item self-rated questionnaire that assesses sleep quality and disturbances over the past month. It comprises seven components-sleep duration, disturbance, latency, daytime dysfunction, efficiency, overall quality, and use of sleep medication-each scored from 0 to 3. The total global score (0-21) reflects overall sleep quality, with 0-7 indicate no or mild sleep difficulty, 8-14 moderate sleep difficulty, and 15-21 severe sleep difficulty.[12]

The statistical analysis was performed using PASW Statistics 18 (Statistical package for social sciences SPSS version 18.0) package India. Data on continuous and categorical scale is presented with appropriate descriptive statistics and graphs. Data were given as mean±SD for numerical data, and number and percentage for categorical data. Descriptive statistics were given as mean, SD. Comparison of endpoints between two time-points were carried out by Student's paired t test and Wilcoxon Signed Rank test wherever applicable. Alpha (α) level of significance was taken as $p<0.05$.

Three analysis sets were considered to represent disposition of the patients safety analysis set (SAF): The SAF included all patients who received at least one dose of the study medication. In SAF, patients were analyzed according to the actual treatment they received. The analysis of all safety variables was based on SAF. ITT set: The ITT set included all recruited patients having at least one post-baseline assessment. Per-protocol (PP) set: Included all ITT patients with complete primary and secondary endpoint values. The PP set included ITT patients who completed study procedures until the time of measurement of said parameter without any major protocol deviations that had an impact on results.

RESULTS

A total of 335 patients were screened, of which 312 participants met the eligibility criteria and were enrolled in the study. Among these, 300 participants completed the 30-day treatment and follow-up assessments, while 12 participants discontinued due to various reasons. The details of participant screening, recruitment, treatment, and follow-up are presented in Figure 1. Confidentiality of all participants was maintained throughout the study period.

The mean age of subjects was 43.13±14.59 years in the [ITT set] and the BMI was 24.66±3.99 kg/m^2. Baseline demographic and clinical characteristics of the study population are summarized in (Table 1).

A total of 57.37% of patients had at least one recorded medical history. Details are summarized in (Table 2). Concomitant medications were used by 178 patients (57.05%). The most frequently prescribed concomitant drug classes were psychoanaleptics (124 patients; 39.74%) and psycholeptics (60 patients; 19.2%), as presented in (Table 3).

In the PP set, the mean baseline PSQI score was 15.17±2.76, which significantly reduced to 11.47±3.73 on day 7 and 5.36±5.02 on day 30 *(*$p<0.001$). In the ITT set, the baseline PSQI score was 15.19±2.75, with corresponding reductions to 11.60±3.74 on day 7 and 5.73±5.58 on day 30 ($p<0.001$).

In the PP set, the mean baseline value of ISI scale was 20.64±5.00. The ISI mean values on day 7 and day 30 reduced to 15.35±4.92 and 6.73±7.63, respectively ($p<0.001$). In the ITT set, the mean baseline value of ISI scale was 20.57±5.00. The ISI mean values on day 7 and day 30 reduced to 15.47±4.96 and 7.18±5.45, respectively ($p<0.001$).

The safety analysis was performed using ESS scale. In the PP set, the mean baseline value of ESS scale was found to be 7.04±6.72. The ESS mean values on day 7 and day 30 reduced to 5.92±6.48 and 4.48±4.72, respectively ($p<0.001$). In the ITT set, the mean baseline value of ESS scale was found to be 6.99±6.68. The ESS mean values on day 7 and day 30 reduced to 5.87±5.63 and 4.48±4.70, respectively ($p<0.001$).

A total of 45 (14.42) patients experienced 60 AEs and of which 44 (14.10) patients reported at least 1 treatment-emergent adverse event (TEAE). Overall, the most frequently reported TEAEs was dizziness (15/312 [4.80%] patients) followed by nausea (12/312 [3.84%] patients), vertigo (6/312 [1.92%] patients), dry mouth and headache (4/312 [1.28] patients). 28 AEs were mild, 30 were moderate and 2 were severe. No serious AEs were reported, and all AEs resolved without sequelae**.**

Overall, treatment with the FDC of ZOLSOMA-5 resulted in significant improvement in sleep quality and daytime alertness, with good tolerability and no serious AEs reported.

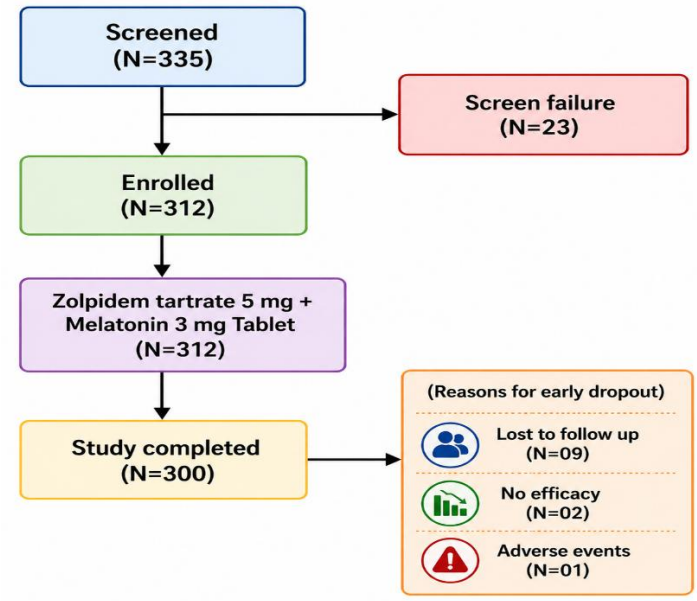

Figure 1: Flowchart of patient disposition.

Table 1: Demographic characteristics-ITT set, (n=312).

Demographics	Total
Age (in years)	43.13±14.59
Height (cm)	162.35±7.41
Weight (kg)	65.18±12.43
BMI (kg/m^2)	24.66±3.99
Gender-count (%)	Males-166 (53.20%), Females-146 (46.79%)
Drinking history-count (%)	Yes=14 (4.48%), No=298 (95.51%)
Smoking history-count (%)	Yes=36 (11.53%), No=276 (88.46%)

Table 2: Medical history, (n=312).

System organ class, preferred term	Investigational drug	Total
Psychiatric disorders	172 (55.1) [170]	172 (55.1) [170]
Major depressive disorder	64 (20.5)	64 (20.5)
Schizophrenia	26 (8.3)	26 (8.3)
Bipolar mood disorder	21 (6.7)	21 (6.7)
Generalised anxiety disorder	14 (4.4)	14 (4.4)
Anxiety disorder	8 (2.5)	8 (2.5)
Psychosis	6 (1.9)	6 (1.9)
Depressive disorder	7 (2.24)	7 (2.24)
Somatic symptom disorder	4 (1.28)	4 (1.28)
OCD	3 (0.9)	3 (0.9)
Dementia	1 (0.3)	1 (0.3)
Recurrent depressive disorder	3 (0.9)	3 (0.9)
Insomnia	2 (0.6)	2 (0.6)
Alcohol induced psychosis	2 (0.6)	2 (0.6)
Mixed anxiety and depressive disorder	2 (0.6)	2 (0.6)
Mixed AD	2 (0.6)	2 (0.6)
Depressive episode	2 (0.6)	2 (0.6)
Panic disorder	1 (0.3)	1 (0.3)
ADHD	1 (0.3)	1 (0.3)
Schizoaffective disorder	1 (0.3)	1 (0.3)
Delusion disorder somatic type	1 (0.3)	1 (0.3)
Depression with psychotic	1 (0.3)	1 (0.3)

Continued.

System organ class, preferred term	Investigational drug	Total
Endocrine disorders	8 (2.25) [8]	8 (2.25) [8]
Diabetes mellitus	8 (2.5)	8 (2.5)
Neurological disorders	7 (2.24) [6]	7 (2.24) [6]
Seizure disorder	3 (0.9)	3 (0.9)
Migraine	2 (0.6)	2 (0.6)
Tension	1 (0.3)	1 (0.3)
Headache	1 (0.3)	1 (0.3)
Muscular disorders	5 (1.6) [5]	5 (1.6) [5]
Hypertension	5 (1.6)	5 (1.6)
Gastrointestinal disorders	1 (0.3) [1]	1 (0.3) [1]
Irritable bowel syndrome	1 (0.3)	1 (0.3)
Metabolic disorders	1 (0.3) [1]	1 (0.3) [1]
Dyslipemia	1 (0.3)	1 (0.3)
Respiratory disorders	1 (0.3) [1]	1 (0.3) [1]
Bronchial asthma	1 (0.3)	1 (0.3)

*Note 1: System Organ Class and Preferred Terms are coded using the MedDRA version 27.
Note 2: All percentages are based on number of patients in SAF.
Note 3: All the SOC counts are represented as: Number of subjects (Percentage) [Event count].
Note 4: Medical history is represented as: Number of subjects (Percentage).

Table 3: Concomitant medication, (n=312).

ATC level 2 text, preferred name	Investigational drug	Total
Psychoanaleptics	124 (39.74)	124 (39.74)
Escitalopram	45 (14.4)	45 (14.4)
Paroxetine	20 (6.41)	20 (6.41)
Mirtazapine	19 (6.08)	19 (6.08)
Sertraline	12 (3.84)	12 (3.84)
Desvenlafaxine	12 (3.84)	12 (3.84)
Vortioxetine	11 (3.52)	11 (3.52)
Venlafaxine	8 (2.56)	8 (2.56)
Amitriptyline	7 (2.24)	7 (2.24)
Fluoxetine	6 (1.92)	6 (1.92)
Donepezil	3 (0.96)	3 (0.96)
Clomipramine	3 (0.96)	3 (0.96)
Dosulepin	3 (0.96)	3 (0.96)
Vilazodone	2 (0.64)	2 (0.64)
Nortriptyline	2 (0.64)	2 (0.64)
Tranylcypromine	2 (0.64)	2 (0.64)
Bupropion	2 (0.64)	2 (0.64)
Duloxetine	2 (0.64)	2 (0.64)
Memantine	1 (0.32)	1 (0.32)
Opipramol	1 (0.32)	1 (0.32)
Methylphenidate	1 (0.32)	1 (0.32)
Tianeptine	1 (0.32)	1 (0.32)
Armodafinil	1 (0.32)	1 (0.32)
Psycholeptics	60 (19.23)	60 (19.23)
Olanzapine	18 (5.76)	18 (5.76)
Haloperidol	11 (3.52)	11 (3.52)
Quetiapine	8 (2.56)	8 (2.56)
Lithium	8 (2.56)	8 (2.56)
Trifluoperazine	7 (2.24)	7 (2.24)
Aripiprazole	5 (1.60)	5 (1.60)
Risperidone	5 (1.60)	5 (1.60)
Tiapride	3 (1.00)	3 (1.00)
Etizolam	1 (0.32)	1 (0.32)
Cariprazine	1 (0.32)	1 (0.32)

Continued.

ATC level 2 text, preferred name	Investigational drug	Total
Antiepileptics	27 (8.65)	27 (8.65)
Divalproex	11 (3.52)	11 (3.52)
Clozapine	7 (2.24)	7 (2.24)
Oxcarbazepine	4 (1.28)	4 (1.28)
Lamotrigine	3 (0.96)	3 (0.96)
Clonazepam	2 (0.64)	2 (0.64)
Sodium Valproate	2 (0.64)	2 (0.64)
Valproic Acid	2 (0.64)	2 (0.64)
Carbamazepine	1 (0.32)	1 (0.32)
Anti-Parkinson drugs	27 (8.65)	27 (8.65)
Trihexyphenidyl	23 (7.37)	23 (7.37)
Pramipexole	3 (0.96)	3 (0.96)
Ropinirole	1 (0.32)	1 (0.32)
Drugs used in diabetes	8 (2.50)	8 (2.50)
Metformin	8 (2.56)	8 (2.56)
Glimepiride	5 (1.60)	5 (1.60)
Vildagliptin	3 (0.96)	3 (0.96)
Sitagliptin	1 (0.32)	1 (0.32)
Calcium channel blockers	4 (1.28)	4 (1.28)
Amlodipine	3 (0.96)	3 (0.96)
Cilnidipine	1 (0.32)	1 (0.32)
Agents acting on renin-angiotensin system	4 (1.28)	4 (1.28)
Telmisartan	3 (0.96)	3 (0.96)
Olmesartan Medoxomil	1 (0.32)	1 (0.32)
Lipid modifying agents	2 (0.64)	2 (0.64)
Atorvastatin	2 (0.64)	2 (0.64)
Other nervous system drugs	2 (0.64)	2 (0.64)
Flunarizine	2 (0.64)	2 (0.64)
Diuretics	2 (0.64)	2 (0.64)
Hydrochlorothiazide	2 (0.64)	2 (0.64)
Beta blocking agents	1 (0.32)	1 (0.32)
Metoprolol	1 (0.32)	1 (0.32)
Antithrombotic agents	1 (0.32)	1 (0.32)
Clopidogrel	1 (0.32)	1 (0.32)
Antidiarrheals, intestinal antiinflammatory or antiinfective agents	1 (0.32)	1 (0.32)
Probiotics	1 (0.32)	1 (0.32)
Analgesics	1 (0.32)	1 (0.32)
Aspirin	1 (0.32)	1 (0.32)
Antihistamins for systemic use	1 (0.32)	1 (0.32)
Levocetirizine	1 (0.32)	1 (0.32)
Drugs for obstructive airway diseases	1 (0.32)	1 (0.32)
Montelukast	1(0.32)	1(0.32)
Antianemic preparations	1 (0.32)	1 (0.32)
Mecobalamin	1 (0.32)	1 (0.32)

*Note 1: ATC level 2 text and Preferred names are coded using WHODD version MAR2019.
Note 2: All percentages based on no. of patients in SAF. Note 3: Concomitant medication is represented as: No. of subjects (Percentage).

Table 4: Change in PSQI score from baseline to day 7 and day 30 (PP and ITT sets).

PSQI categories/ time points	Baseline	Day 7	Day 30	Baseline	Day 7	Day 30
	PP set, (n=300)			**ITT set, (n=312)**		
0=No sleep difficulty	0 (0.0%)	1 (0.3%)	7 (2.3%)	0 (0.0%)	1 (0.3%)	7 (2.2%)
1-7=Mild sleep difficulty	2 (0.7%)	47 (15.7%)	232 (77.3%)	2 (0.6%)	47 (15.1%)	232 (74.4%)
8-14=Moderate sleep difficulty	102 (34.0%)	191(63.7%)	59 (19.7%)	106 (34.0%)	197 (63.1%)	65 (20.8%)

Continued.

PSQI categories/ time points	Baseline	Day 7	Day 30	Baseline	Day 7	Day 30
	PP set, (n=300)			ITT set, (n=312)		
15-21=Severe sleep difficulty	196 (65.3%)	61 (20.3%)	2 (0.7%)	204 (65.4%)	67 (21.53%)	8 (2.8%)
Comparison of baseline with day 7 and day 30		<0.001	<0.001		<0.001	0.001

*Each value is expressed as patient number (percentage) and statistical analysis were performed by using Wilcoxon Signed Rank test.

Table 5: Change in ISI score from baseline to day 7 and day 30 (PP and ITT sets).

ISI categories/time points	Baseline	Day 7	Day 30	Baseline	Day 7	Day 30
	PP set, (n=300)			ITT set, (n=312)		
0-7=No clinically significant insomnia	1 (0.3%)	12 (4.0%)	177 (59.0%)	1 (0.3%)	12 (3.8%)	177 (56.7%)
8-14=Subthreshold insomnia (Mild)	39 (13.0%)	128 (42.7%)	104 (34.7%)	42 (13.5%)	131 (42.0%)	107 (34.3%)
15-21=Clinical insomnia (Moderate)	128 (42.7%)	129 (43.0%)	18 (6.0%)	132 (42.3%)	133 (42.6%)	22 (7.1%)
22-28=Clinical insomnia (Severe)	132 (44.0%)	31 (10.3%)	1 (0.3%)	137 (43.9%)	36 (11.5%)	6 (1.9%)
Comparison between baseline and day 7 or 30.		<0.001	<0.001		<0.001	<0.001

*Each value is expressed as patient number (percentage) and statistical analysis were performed by using Wilcoxon Signed Rank test.

Table 6: Change in ESS score from baseline to day 7 and day 30 (PP and ITT sets).

ESS categories/ time points	Baseline	Day 7	Day 30	Baseline	Day 7	Day 30
	PP set (n=300)			ITT set (n=312)		
0-5=Low daytime sleepiness (Normal)	143 (47.7%)	143 (47.7%)	184 (61.3%)	149 (47.8%)	149 (47.8%)	190 (60.9%)
6-10=High daytime sleepiness (Normal)	71 (23.7%)	92 (30.7%)	82 (27.3%)	75 (24.0%)	97 (31.1%)	87 (27.9%)
11-12=Mild sleepiness	26 (8.7%)	29 (9.7%)	18 (6.0%)	27 (8.7%)	29 (9.3%)	18 (5.8%)
13-15=Moderate sleepiness	21 (7.0%)	19 (6.3%)	8 (2.7%)	21 (6.7%)	20 (6.4%)	9 (2.9%)
16-24=Severe sleepiness	39 (13.0%)	17 (5.7%)	8 (2.7%)	40 (12.8%)	17 (5.4%)	8 (2.6%)
Comparison between baseline and day 7 or 30.		<0.001	<0.001		<0.001	<0.001

*Each value is expressed as patient number (percentage) and statistical analysis were performed by using Wilcoxon Signed Rank test.

DISCUSSION

Sleep disturbances such as insomnia commonly co-occur with mental health conditions like depression and anxiety. Insomnia symptoms have traditionally been viewed as secondary. The implication is that insomnia is either a symptom or consequence of other mental health difficulties. Because of its nonspecific nature across diagnoses, treatment of insomnia has often been neglected in patient care.[13] Ongoing research highlights the bidirectional relationship between sleep and mental health, suggesting that improving sleep can beneficially impact psychiatric disorders. Combination products, the FDCs, are combinations of two or more active drugs in a single dosage form.[14] In this regard, combination therapies targeting multiple mechanisms may offer improved efficacy and tolerability compared with monotherapy.

The zolpidem-melatonin FDC is designed to improve sleep quality while minimizing daytime drowsiness, cognitive impairment, and motor incoordination associated with higher doses of zolpidem.[15] Zolpidem and other Benzodiazepine - receptor agonist (BZDRAs) dose dependently impair memory at their peak sleep-inducing effects.[16,17] The use of melatonin is preferable as it does not impair memory to the same extent as somnogenically equivalent doses of zolpidem. Higher dose of melatonin (>5 mg) slows response speed and also reduces accuracy.[18-24] Combining low-dose zolpidem with

melatonin leverages their complementary properties, enhancing sleep without the performance impairments seen with higher-dose zolpidem.

The objective of the present study was to evaluate the efficacy and safety of a FDC of melatonin and zolpidem in improving quality of sleep without exacerbating the side effects reported previously with higher dose of zolpidem. The study population consisted of patients experiencing sleep disturbances in the context of comorbid psychiatric disorders. The most prevalent diagnosis among participants was major depressive disorder, followed by schizophrenia, bipolar disorder, and generalized anxiety disorder. The therapeutic effect of the combination (ZOLSOMA-5) on sleep parameters was assessed using validated instruments-the PSQI, ISI, and ESS-while safety evaluation focused on recording the incidence, nature, and type of AEs.

The administration of the FDC resulted in a significant improvement in overall sleep quality throughout the treatment period, as reflected in the change in PSQI scores for both the ITT and PP populations. Participants showed progressive improvement from baseline to subsequent follow-up visits. The higher score is indicative of severe sleep difficulty, and consequently, a reduction in score represents an improvement in sleep quality. The difference from baseline was significant at $p<0.001$. Our findings are consistent with those of Shahrokhi et al who document significant improvement in sleep quality over a 4 week period with either of zolpidem or melatonin.[25]

The improvement in sleep quality observed with the zolpidem–melatonin FDC was also evident in the ISI scores. Both the ITT and PP populations demonstrated a steady decline in insomnia severity from baseline to subsequent evaluation points. These reductions indicate a marked improvement in insomnia severity. A reduction of ≥ 8 points suggests at least moderate improvement after treatment with the FDC.[26,27] The difference from baseline was statistically significant $p<0.001$. A similar improvement in ISI score was earlier documented by Castro et al with zolpidem, used either orally or sublingually. Melatonin has also been shown to reduce ISI scores in patients with bipolar illness.[28,29]

Regarding safety analysis, the ESS is a simple, self-administered questionnaire which is shown to provide a measurement of the subject's general level of daytime sleepiness. Any reduction or improvement in day-time sleepiness is a reflection of better sleep quality at night. In the present study the combination of ZOLSOMA-5 significantly reduced the ESS score from baseline to day 30. This reduction was significant at $p<0.001$. In a study utilizing extended-release zolpidem 12.5 mg the improvement in ESS score took much longer as compared to the combination FDC. The improvement with zolpidem + melatonin FDC probably could be attributed to circadian rhythm regularizing activity of melatonin.

The most frequently reported AEs with the combination were giddiness (4.48%) and nausea (4.16%). A search of available literature suggests giddiness in 5% of patients taking zolpidem and 0.74% in individuals taking melatonin. Furthermore, the incidence of nausea with zolpidem is documented to be 7% and that with melatonin is said to be the least effected.[30,31] The other reported side effects included vertigo (1.92%), headache and dryness of mouth (1.28%). Two patients (0.64%) reported diarrhea and increased appetite with the combination. The available literature documents vertigo incidence of 2% with zolpidem and about 19% of patients report headache with zolpidem.[30] These two AEs appear to be due to zolpidem or the concomitant therapies which included SSRIs and antipsychotics, as they have not been reported with melatonin. Diarrhoea and altered appetite has also been reported with zolpidem with an incidence of 3% and 1%, respectively.[30] Two patients reporting altered appetite were also on olanzapine, a drug known to increase body weight, and two patients experiencing tremors were on concomitant treatment with divalproate, olanzapine and desvenlafaxine.[32] These concomitant medications have also been reported to cause tremors.[33-35]

In the present study one patient with bipolar illness reported polyuria, which can be attributed to the lithium treatment. Polyuria is the most common complication in an otherwise asymptomatic patient who has a plasma lithium level consistent with therapeutic dose.[36] Other reported AEs included itching, chest pain, metallic taste, dry lips, leg shaking, abdominal pain and lethargy. Most of the AEs experienced were mild and transient in nature, and were reported in the first week of the treatment initiation and resolved by the subsequent visit.

More than half of the study population had at least one recorded medical history, predominantly psychiatric disorders, and a similar proportion of patients received concomitant medications, most commonly psychoanaleptics and psycholeptics. Studies have shown that treating insomnia leads to better outcomes and improvement in co-existing psychiatric disorders. To achieve optimal treatment outcomes in people with comorbid psychiatric illness and insomnia, the clinician should target both disorders.[37]

The zolpidem-melatonin FDC was generally well tolerated. The most common AEs were mild CNS-related effects, consistent with the known profiles of both drugs. One patient discontinued due to giddiness and restlessness, nine were lost to follow-up, and two withdrew citing lack of efficacy.

From the study it is evident that the FDC of zolpidem + melatonin is efficacious in improving sleep quality and total duration of sleep in patients experiencing sleep difficulty or insomnia with comorbidities.

Despite the promising findings, this study has several limitations. The open-label, single-arm design without a control group limits the ability to definitively attribute

improvements to the intervention and raises the possibility of placebo effects. The short duration of 30 days precludes assessment of long-term efficacy and safety, including tolerance and dependency potential. The reliance on self-reported scales may introduce reporting bias, and objective sleep measures were not employed. These limitations should be considered when interpreting the results, and future randomized controlled trials with longer follow-up and objective assessments are warranted to confirm and extend these findings.

CONCLUSION

The FDC of ZOLSOMA-5 was found to be safe, well-tolerated, and effective in improving sleep quality, reducing insomnia severity, and alleviating daytime sleepiness in patients with comorbid psychiatric disorders. The combination leveraged the complementary mechanisms of ZOLSOMA-5, providing significant therapeutic benefits while minimizing adverse effects typically associated with higher-dose zolpidem. These findings suggest that this FDC represents a promising treatment option for managing sleep disturbances in psychiatric populations, supporting both short-term efficacy and favourable tolerability.

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