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A phase 1 double-blind, placebo-controlled study of zuranolone (SAGE-217) in a phase advance model of insomnia in healthy adults

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Abstract

Objective: To evaluate single zuranolone (SAGE-217) 30 or 45 mg doses in a 5-h phase advance insomnia model.

Methods: In this double-blind, three-way crossover study, healthy adults received placebo ($n = 41$), zuranolone 30 mg ($n = 44$), and zuranolone 45 mg ($n = 42$) across three treatment periods. Sleep was assessed by polysomnography and a postsleep questionnaire. Next-day residual effects and safety/tolerability were evaluated.

Results: Compared with placebo, zuranolone resulted in significant improvements in median sleep efficiency (30 mg, 84.6%; 45 mg, 87.6%; placebo, 72.9%; $p < 0.001$ for both doses), wake after sleep onset (WASO; 30 mg, 55.0 min; 45 mg, 42.5 min; placebo, 113.0 min; $p < 0.001$ for both doses), duration of awakenings (30 mg, 4.2 min, $p < 0.001$; 45 mg, 3.7 min, $p = 0.001$; placebo, 7.4 min), and total sleep time (TST; 30 mg, 406.3 min; 45 mg, 420.3 min; placebo, 350.0 min; $p < 0.001$ for both doses). Subjective endpoints (WASO, TST, sleep latency, sleep quality) also improved relative to placebo. Zuranolone was generally well tolerated, and the most common adverse events (≥2 participants, any period) were headache and fatigue.

Conclusion: Zuranolone improved sleep measures versus placebo in a phase advance model of insomnia in healthy adults, supporting future studies in patients with insomnia disorder.

KEYWORDS
insomnia, polysomnography, SAGE-217, sleep phase advance, zuranolone

1 | INTRODUCTION

Approximately 30% of the adult United States (US) population experiences issues with the quality and quantity of their sleep (National Institutes of Health, 2005; National Sleep Foundation, 2002, 2005), and approximately 10% of the US adult population reports sleep problems severe enough to be considered insomnia disorder (American Psychiatric Association, 2013; LeBlanc et al., 2009; National Institutes of Health, 2005). In addition, approximately 60%–80% of patients with insomnia experience comorbid psychiatric conditions

(Ford & Kamerow, 1989; Ohayon et al., 2000; Stewart et al., 2006; Weissman et al., 1996), and sleep disruptions can lead to significantly lower positive mood (Finan et al., 2015). In particular, people with self-reported sleep disruptions have been reported as 9.82 times more likely to have comorbid major depressive disorder (MDD) and 17.35 times more likely to experience clinically significant anxiety (Taylor et al., 2005). Insomnia can be chronic (i.e., lasting longer than three months) or short-term (i.e., lasting less than 3 months) and is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition based on a variety of sleep-related symptoms, including difficulty in falling asleep, difficulty in maintaining sleep, and early waking, accompanied with clinically significant distress or functional impairment (American Psychiatric Association, 2013; National Institutes of Health, 2005). Insomnia symptoms—especially difficulty in initiating sleep—in adults and adolescents, are associated with reduced quality of life and increased mortality (Paiva et al., 2015; Parthasarathy et al., 2015; Scalo et al., 2014), and individuals who report difficulty returning to sleep after awakening (i.e., longer mean durations of awakenings [mDURAWs]) in the presence of other insomnia symptoms, are more likely to report daytime impairment and seek treatment for their sleep disorder (Ohayon, 2009; Ohayon et al., 2010).

Sleep disruptions and general insomnia are linked to greater brain metabolism and hyperactivity of neural circuits during normal sleep architecture (Nofzinger et al., 2004). Gamma-aminobutyric acid (GABA) is the primary mediator of inhibitory neurotransmission in the central nervous system and is intimately associated with the regulation of sleep and wake cycles (Wisden et al., 2017). Synaptic $GABA_A$ receptors ($GABA_AR$s) have rapid kinetics, low sensitivity to GABA, and prompt desensitization, enabling them to conduct fast inhibitory postsynaptic events that are typical for phasic inhibition (Brickley et al., 1999). Extrasynaptic $GABA_AR$s are activated by low concentrations of GABA neurotransmitter, which mediate persistent tonic inhibition (Stell & Mody, 2002). Tonic inhibition represents a large fraction of GABA signaling and can approach 80% of total GABA-mediated transmission in regions such as the thalamus (Belelli et al., 2005). Previous studies have reported a relationship between GABA activity in the hypothalamus and maintenance of wakefulness (Lin et al., 1989; Nitz & Siegel, 1996), and sleep-active GABAergic neurons in the brain inhibit wake-active neurons to promote sleep (Chung et al., 2017; Lin et al., 1989; Nitz & Siegel, 1996; Sherin et al., 1998; Uygun et al., 2016). The involvement of GABA signaling in sleep suggests that positive allosteric modulation of $GABA_AR$ presents a potential mechanism of action for insomnia pharmacotherapies (Wisden et al., 2017).

Zuranolone (SAGE-217; 3α-hydroxy-3β-methyl-21-(4-cyano-1H-pyrazol-1′-yl)-19-nor-5β-pregnan-20-one) is a rationally designed, orally bioavailable, investigational neuroactive steroid, and like other members of the neuroactive steroid family, such as allopregnanolone, it is a positive allosteric modulator (PAM) for both synaptic and extrasynaptic $GABA_AR$, making it pharmacologically distinct from current insomnia pharmacotherapies, including benzodiazepines and "Z-drugs," which target only synaptic $GABA_AR$s (Hosie et al., 2006; Martinez Botella et al., 2017). Neuroactive steroid sites on $GABA_AR$s are distinct from and do not overlap with the binding sites for the benzodiazepines and barbiturates (Laverty et al., 2017; Löscher & Rogawski, 2012). The pharmacokinetics of zuranolone are suitable for once daily dosing (Hoffmann et al., 2019), and zuranolone has previously been examined in Phase 2 (Gunduz-Bruce et al., 2019) and Phase 3 (Clayton, 2020) trials for MDD and a Phase 3 trial in postpartum depression (Deligiannidis et al., 2021). Zuranolone represents an opportunity to examine the role that positive allosteric modulation of both synaptic and extrasynaptic $GABA_AR$ plays in the regulation of sleep as well as implications for the treatment of insomnia and sleep disruptions.

Acute sleep disturbance can be studied using the 5-h phase advance model of transient insomnia in healthy participants. The overall size of the phase advance increases wakefulness and allows for the reduction of steady sleep pressure while the circadian rhythm for wakefulness is strong, and prior studies have demonstrated that this insomnia model can be modulated pharmacologically (Horoszok et al., 2014; Rosenberg et al., 2014). In the 5-h phase advance model, multiple sleep parameters, including wake after sleep onset (WASO), total sleep time (TST), and sleep efficiency (SE) are negatively affected, and these disruptions can be mitigated by sedative and hypnotic agents, such as nonbenzodiazepines (e.g., lorediplon) and Z-drugs (e.g., zolpidem) (Horoszok et al., 2014). Furthermore, physiological similarities between insomnia disorder and phase advance transient insomnia models have been reported (Bonnet & Arand, 2003).

This Phase 1, double-blind, randomized trial in healthy adults used a 5-h phase advance model to evaluate the effects of zuranolone compared with placebo on transient insomnia.

2 | METHODS

2.1 | Study design

This randomized, double-blind, single-dose, placebo-controlled study (Clinicaltrials.gov identifier: NCT03284931) was conducted at a certified sleep laboratory in the US. The procedures of this study were in compliance with the ethical principles from the Helsinki Declaration of 1975, as revised in 1983, and was consistent with the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines, as well as all applicable regulatory requirements. The study was approved by an institutional review board. Written informed consent was obtained at screening and was required for enrollment.

2.2 | Study population

Eligible participants were healthy, ambulatory, men and women between the ages 18 and 64, with body weight ≥50 kg and a body mass index (BMI) between 18 and 32 kg/m^2. Participants were required to have a Pittsburgh Sleep Quality Index score of ≤5 and an Epworth Sleepiness Scale score of ≤10, indicating normal sleep quality (SQ) and lack of excessive daytime sleepiness. All participants completed a

sleep diary for a minimum of six consecutive days between screening and qualification polysomnography (PSG), confirming habitual bed and rise times within 1-h time frames and a routine time in the bed of 7–9 h. During the PSG qualification visit (5-h, phase advanced), participants were required to have a PSG-assessed WASO of more than 45 min, an apnea-hypopnea index of less than 10, and a periodic limb movement arousal index of less than 10.

Participants agreed to adhere with behavioral restrictions, including abstinence from using tobacco, alcohol, and recreational drugs; maintenance and documentation of normal sleep habits; and refraining from working night shifts, napping, or flying more than 1 time zone away from the study site (full details in Supporting Information Methods S1). Female participants were required to use an approved form of contraception (full list in Supporting Information Methods S2) during the study and for 30 days following the last dose of the study drug.

Exclusion criteria included: a clinically significant abnormal finding during the physical examination at the screening visit; a positive drug and/or alcohol test at screening or the PSG qualification visit; consumption of excessive amounts of caffeine (defined as >500 mg/day) within 30 days prior to the screening visit; use of strong inhibitors and/or inducers of cytochrome P450 3A4 within the prior 14 days or 5 half-lives (whichever is longer); consumption of grapefruit juice, grapefruit, Seville oranges, St. John's Wort, or products containing these within 30 days prior to the screening visit; night shift work and flying more than 1 time zone within 30 days prior to the screening visit. Full exclusion criteria are provided in the Supporting Information Methods S3.

2.3 | Procedures

The study utilized a double-blind, placebo-controlled, six-sequence, three-way crossover design (Figure 1), with a 7-day washout period between treatments. Participants arrived at the clinic approximately 7 h prior to their habitual bedtime. Eligibility criteria were confirmed, and participants were randomized (1:1:1:1:1:1) to 1 of 6 possible study drug administration sequences.

A single dose of double-blind study drug (zuranolone 30 mg, zuranolone 45 mg, or matching placebo) was administered as three capsules to the participant, at the site, on Days 1, 8, and 15. Zuranolone blinded study drug or placebo was administered with food 30 (±15) min prior to lights out.

Lights out and PSG recording began 5 h (±30 min) before the participants' habitual bedtime. Participants were required to remain in bed for 8 h, after which the lights were turned on, and they were awakened, if asleep. Following lights on, PSG recording continued for 5 (±1) min of quiet wakefulness, and participants completed a postsleep questionnaire 30 min after the end of the recording. Discharge from the clinic occurred at or after 6:00 a.m. when the safety assessments did not reveal evidence of impairment and at the investigator's discretion. Participants resumed normal sleep patterns and maintained a sleep diary during the 1-week washout periods between treatments. A follow-up visit was conducted 7 days (±1 day) after the final administration of study drug, and a follow-up telephone call (Visit 8) occurred 7 days (±1 day) after the follow-up visit.

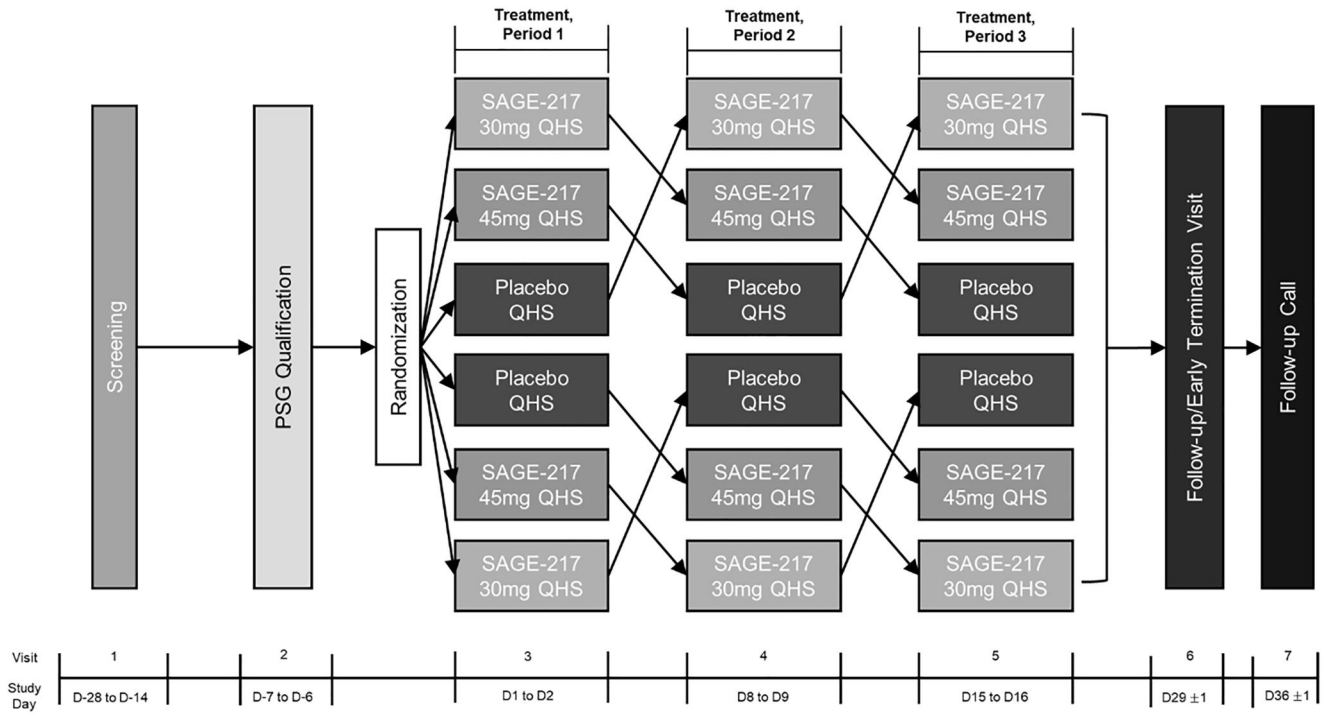

FIGURE 1 Study design. The study used a randomized, six-sequence, crossover design in 45 participants. QHS, quaque hora somni (i.e., nightly at bedtime)

2.4 | Assessments

2.4.1 | Safety and tolerability

The Safety Set included all participants ($n = 45$) administered study drug. Postwaking safety and tolerability assessments and next day effect assessments were performed, including reporting of treatment-emergent adverse events (TEAEs), vital signs, 12-lead electrocardiograms, and the Columbia Suicide Severity Rating Scale. Next day effect assessments included the Karolinska Sleepiness Scale (KSS), the Digit Symbol Substitution Test (DSST) data, Romberg's test, and heel-to-toe walking. Both the KSS and DSST were completed within 30 min (±15) before initiation and after completion of PSG.

2.4.2 | Efficacy

The Efficacy Set was based on a modified intent-to-treat (ITT) population and included all participants in the Safety Set who had at least one postdose PSG datapoint. The primary endpoint was objective SE, defined as the percentage of time in bed spent asleep, determined by an 8-h overnight PSG recording. Secondary endpoints consisted of both objective (i.e., by PSG) and subjective (i.e., by postsleep questionnaire) measurements, including WASO (objective and subjective); TST (objective and subjective); latency to persistent sleep (LPS; objective) and sleep latency (SL; subjective); SQ (subjective); number of awakenings (NAW; objective) and mDURAWs (objective); time spent in sleep stages (i.e., N1, N2, N3, and R), and latency to stage R sleep.

2.5 | Statistical methods

Assuming a two-sided *t*-test at an alpha level of 0.05, a sample size of 31 evaluable participants would provide 80% power to detect a difference of 8 percentage points between zuranolone and placebo for SE. The trial was planned to recruit 42 participants to obtain at least 31 evaluable participants assuming a nonevaluability rate of 20%. Forty-five participants were enrolled.

The primary and secondary efficacy endpoints were both analyzed using a mixed effects model for repeated measures. The model included treatment, treatment sequence, period, and screening SE as fixed effects and participant nested within the sequence as random effect. An unstructured covariance structure was used to model within-participant errors. The residuals from the mixed-effect model were then tested for normality using the Shapiro–Wilk W-test. If the normality assumption was met, the model-based point estimates (least-squares [LS] means) of zuranolone 30 mg versus placebo and zuranolone 45 mg versus placebo together with the 95% confidence intervals, and *p* values from the mixed-effect model for repeated measures were reported. If the normality assumption was not met, nonparametric tests were used. Friedman's test was used to test the overall treatment effect among the three treatment groups and treatment comparisons (zuranolone 30 mg vs. placebo and zuranolone 45 mg vs. placebo) were assessed using the Wilcoxon signed-rank test on the within-participant differences. No multiplicity adjustment for the efficacy analyses was performed. Nominal *p* values with confidence intervals are presented.

3 | RESULTS

3.1 | Participants and treatment

Forty-five participants were randomized to this trial. Demographic and baseline characteristics are provided in Table 1. Thirty-six participants (80%) completed all periods of the study. Nine participants discontinued at the following periods for the stated reasons: four participants during the double-blind period (scheduling conflicts [$n = 3$], positive cotinine drug test [$n = 1$]), five participants completed all treatment periods, but did not return for the follow-up visit (lost to follow-up).

3.2 | Objective assessments by PSG

Both zuranolone doses (30 or 45 mg) significantly improved objective SE (measured by PSG) with medians of 84.6% and 87.6%, respectively, compared to 72.9% for placebo ($p < 0.001$ for both doses). Secondary endpoints measured by PSG are summarized in Table 2, including WASO, TST, LPS, NAW, and mDURAW. In addition to the effects on SE, zuranolone (30 and 45 mg) reduced median WASO to 55.0 and 42.5 min, respectively, compared to 113.0 min for placebo ($p < 0.001$ for each dose). Furthermore, TST was higher with zuranolone treatment (a median of 406.3 min for the 30-mg group and 420.3 min for the 45-mg group, compared with a median of 350.0 min in placebo; both $p < 0.001$). Zuranolone reduced mDURAWs with medians of 4.3 min ($p < 0.001$; 30 mg) and 3.7 min ($p = 0.001$; 45 mg) compared with 7.4 min for placebo. No significant differences between zuranolone treatment at either dose and placebo were observed for LPS and NAW.

The potential of zuranolone to affect sleep architecture was also examined via PSG (Table 3a). The LS mean time spent in Stage N2 and Stage N3 significantly increased with zuranolone treatment at both 30 mg (N2: 258.2 min, $p < 0.001$; N3: 68.4 min, $p = 0.004$) and 45 mg (N2: 266.8 min, $p < 0.001$; N3: 74.7 min, $p < 0.001$) doses compared with placebo treatment (N2: 192.3 min; N3: 56.1 min). No significant difference in the time spent in N1 or stage R sleep was observed at either zuranolone dose compared with placebo. Latency to stage R sleep was determined from the number of non-R stage sleep epochs from lights off to the first epoch of stage R sleep. A significant increase in latency to stage R sleep was observed in both zuranolone groups, with median values of 159.0 min ($p = 0.025$) and 220.5 min ($p < 0.001$) for the 30- and 45-mg doses, respectively, compared with 120.0 min for placebo.

TABLE 1 Participant demographics

Baseline characteristics	All participants (n = 45)
Age in years, mean (*SD*)	37.1 (11.17)
Female	18 (40%)
Male	27 (60%)
Race	
Asian	2 (4.4%)
Black or African American	25 (55.6%)
Native Hawaiian or other Pacific Islander	1 (2.2%)
White	8 (17.8%)
Other	8 (17.8%)
Multiple	1 (2.2%)
Ethnicity	
Hispanic or Latino	16 (35.6%)
Mean body mass index	26.8 (3.08)
Baseline measurements	**Mean (*SD*)**
Epworth Sleepiness Scale	2.9 (1.61)
Pittsburgh Sleep Quality Index	1.2 (0.81)
Wakefulness After Sleep Onset	145.83 (67.934)
Apnea-Hypopnea Index	2.82 (2.480)
Periodic Limb Movement Arousal Index	0.26 (0.480)

Note: Data for participants in the study are listed as mean (SD) or *n* (%).

When sleep stage was assessed by percentage of time asleep, zuranolone administration at either dose was associated with significant increases in the percentage of time (Table 3b) spent in stage N2 (LS means: placebo = 60.0%, zuranolone 30 mg = 65.2%, and zuranolone 45 mg = 66.0%; $p < 0.001$ for either dose vs. placebo). Non-significant increases were observed in stage N3 (medians: placebo 17.0%, zuranolone 30 mg = 17.9%, and zuranolone 45 mg = 18.5%). Corresponding decreases were observed in the time spent in stages N1 (medians: placebo 5.7%, zuranolone 30 mg = 3.8%, and zuranolone 45 mg = 4.7%; $p < 0.05$ for either dose vs. placebo) and R (LS means: placebo = 16.2%, zuranolone 30 mg 12.6%, and zuranolone 45 mg = 10.7%; $p < 0.001$ for either dose vs. placebo).

3.3 | Subjective assessments

Subjective WASO (sWASO), TST (sTST), SL (sSL), and SQ (sSQ) were also measured using a postsleep questionnaire. All measures improved significantly, supporting the objective PSG-generated data (Table 4). Both zuranolone 30 mg (11.7 min median difference, $p = 0.026$) and 45 mg (15.0 min median difference, $p = 0.001$) groups showed significant improvement in sTST versus placebo. Each zuranolone dose group also had a −10.0 min ($p < 0.001$) median difference in sWASO and a 1 point ($p < 0.001$) median difference in sSQ score compared with placebo. A significant decrease in sSL was also observed for the 45-mg group, with a 5 min median difference from placebo ($p < 0.001$).

3.4 | Safety and tolerability assessments

Overall, zuranolone was generally well-tolerated, with no serious or severe adverse events, and there were no discontinuations due to adverse events. All TEAEs were mild. TEAEs were reported in 9.8% (4/41) of participants during the placebo treatment period, 11.4% (5/44) of participants during the zuranolone 30-mg treatment period, and 4.8% (2/42) of participants during the zuranolone 45-mg treatment period (Table 5). The most frequent TEAEs (≥2 participants in any period) were headache (placebo, $n = 2$) and fatigue (zuranolone 30 mg, $n = 2$) (Table 5). All other TEAEs were reported by 1 participant each (Table S1).

3.5 | Next-day assessments

There were no significant differences in the KSS, DSST, and Romberg for zuranolone versus placebo, although more participants from the 45 mg zuranolone treatment group reported signs of sleepiness at the post-PSG assessment. A summary of KSS and DSST assessments is provided in Table S2.

TABLE 2 Efficacy outcomes

		Placebo (n = 41)	Zuranolone 30 mg (n = 44)			Zuranolone 45 mg (n = 42)		
Measure	Baseline (median)	Median (min, max)	Median (min, max)	Diff. versus placebo median (Q1, Q3)	p Value	Median (min, max)	Diff. versus placebo median (Q1, Q3)	p Value
SE	66.04	72.92 (7.7, 92.6)	84.64 (45.8, 97.4)	11.35 (1.98, 26.15)	<0.001	87.55 (54.1, 98.0)	12.61 (3.65, 33.13)	<0.001
WASO (min)	134.00	113.00 (16.0, 304.0)	55.00 (10.0, 250.5)	−22.00 (−118.00, −6.00)	<0.001	42.50 (5.0, 208.0)	−55.50 (−105.00, −14.00)	<0.001
TST (min)	317.00	350.00 (37.0, 444.5)	406.25 (220.0, 467.5)	54.50 (9.50, 125.50)	<0.001	420.25 (259.5, 470.5)	60.50 (17.50, 159.00)	<0.001
LPS (min)	28.50	12.50 (0.0, 305.0)	13.25 (0.0, 91.5)	−1.50 (−14.50, 5.00)	0.208	14.25 (1.0, 71.5)	−1.00 (−13.50, 8.50)	0.264
NAW	9.00	8.0 (1, 41)	8.0 (1, 21)	−1.00 (−4.00, 4.00)	0.963	7.0 (0, 32)	−2.00 (−5.00, 2.00)	0.352
mDURAW (min)	9.36	7.38 (1.5, 169.5)	4.23 (1.4, 92.5)	−3.43 (−15.10, 0.88)	<0.001	3.67 (0.0, 30.5)	−1.50 (−13.41, 0.86)	0.001

Note: Treatment versus placebo comparisons of polysomnography (PSG) data was assessed using a Wilcoxon signed-rank test on the within-participant difference. SE was the primary efficacy endpoint. p values are not adjusted for multiplicity.

Abbreviations: LPS, latency to persistent sleep; mDURAW, mean duration of awakening; NAW, number of awakenings; SE, sleep efficiency; TST, total sleep time; WASO, wakefulness after sleep onset.

4 | DISCUSSION

This study is the first randomized, placebo-controlled clinical trial to evaluate single doses of zuranolone in a transient insomnia model in healthy adults. Using a 5-h phase advance model of transient sleep disturbance, acute treatment with both the 30- and 45-mg doses of zuranolone significantly improved objective measures of SE, duration, maintenance, and as well as subjective measures of SQ when compared with placebo.

Transient insomnia models can help predict the potential efficacy of new therapeutics for the treatment of sleep disruption in patients with insomnia disorder by providing a common generic pathway to insomnia (Perlis et al., 2011). Studies have also used the predictive nature of the phase advance models (3-, 4-, or 5-h phase advances) to evaluate the effect of potential insomnia pharmacotherapies on sleep stages and sleep maintenance (Furey et al., 2014; Horoszok et al., 2014; Rosenberg et al., 2014; Roth et al., 2010; Svetnik et al., 2010). Longer phase advance models of insomnia like the 5-h model are well suited to measure the effect of interventions on sleep maintenance (Horoszok et al., 2014; Roth et al., 1995; Staner et al., 2009; Stone et al., 2002; Walsh et al., 2007), whereas shorter (2–3 h) phase advanced models of insomnia are more effective at disrupting sleep induction. There was no significant change in the latency to sleep onset (LPS) observed at either dose of zuranolone in this 5-h phase advance model of insomnia. Assessment of any potential effect of zuranolone on the rate of sleep induction must await future clinical trials in subjects with insomnia disorders.

Notably, zuranolone is the first neuroactive steroid PAM of both synaptic and extrasynaptic $GABA_AR$s to be examined in a human insomnia model. The observed effects of zuranolone in this model are consistent with its primary pharmacology as a $GABA_AR$ PAM. $GABA_AR$ synaptic PAMs, such as benzodiazepines and Z-drugs, have been previously studied in insomnia models for their effects on sleep (Horoszok et al., 2014; Kanno et al., 1993; Walsh et al., 1990). Selective activation of $GABA_A$ synaptic or extrasynaptic receptors on sleep was specifically examined by Walsh et al. (2007) in a 4-h phase advance PSG study. Gaboxadol, a selective extrasynaptic $GABA_AR$ agonist, and zolpidem, a selective modulator of synaptic $GABA_AR$s, were compared to placebo for their effects on sleep parameters and sleep architecture. Both zolpidem and gaboxadol increased TST, and reduced WASO and LPS measures. Changes in sleep architecture included an increase in the number of minutes spent in slow-wave sleep and Stage 2 sleep, but had no significant effect on time in Stage 1 and REM sleep. Latency to REM sleep was reduced only following treatment with in an intermediate dose of gaboxadol and and was not observed with zolpidem (Walsh et al., 2007).

One observation of the study was a significant increase in TST, primarily as a result of more time spent in the N2 phase of NREM sleep. However, although there was no significant change to the number of minutes observed in REM sleep following zuranolone administration, the potential for direct effects on REM sleep cannot be completely ruled out by the current study. More NREM activity resulted in an expansion of TST but not in an expansion of REM sleep, so although the

TABLE 3A Time spent in each sleep stage determined by polysomnography

Measure	Placebo (n = 41)	Zuranolone 30 mg (n = 44)			Zuranolone 45 mg (n = 42)		
	LS mean (SE)	LS mean (SE)	Diff. vs. placebo LS mean (95% CI)	p Value	LS mean (SE)	Diff. vs. placebo LS mean (95% CI)	p Value
Stage N1 (min)	20.67 (1.762)	20.11 (1.712)	−0.56 (−3.76, 2.64)	0.727	19.58 (1.743)	−1.09 (−4.29, 2.11)	0.499
Stage N2 (min)	192.30 (7.890)	258.16 (7.579)	65.86 (47.16, 84.57)	<0.001	266.79 (7.776)	74.49 (55.71, 93.27)	<0.001
Stage N3 (min)	56.12 (4.982)	68.38 (4.861)	12.26 (4.06, 20.47)	0.004	74.71 (4.937)	18.59 (10.40, 26.78)	<0.001
Stage R (min)	50.59 (3.278)	50.15 (3.151)	−0.45 (−8.01, 7.11)	0.906	43.54 (3.232)	−7.05 (−14.63, 0.53)	0.068
	Median (range)	Median (range)	Diff. vs. placebo median (Q1, Q3)	p Value	Median (range)	Diff. vs. placebo median (Q1, Q3)	p Value
Latency to stage R (min)	120.0 (3, 429)	159.0 (4, 528)	55.00 (−30.00, 92.00)	0.025	220.5 (11, 508)	95.00 (17.00, 211.00)	<0.001

Note: Stages N1, N2, N3, and stage R least-squares means and p- values were calculated from a mixed model for repeated measures. Latency to stage R sleep are presented as median (range) or median difference (Q1 − Q3 difference), with a statistical comparison to placebo using a Wilcoxon signed-rank test on the within-participant differences. p Values are not adjusted for multiplicity.

Abbreviations: CI, confidence interval; LS mean, least-squares mean.

TABLE 3B Percentage of time spent in each sleep stage as determined by polysomnography

Measure	Placebo (n = 41)	Zuranolone 30 mg (n = 44)			Zuranolone 45 mg (n = 42)		
	Median (range)	Median (range)	Diff. versus placebo median (Q1, Q3)	p Value	Median (range)	Diff. versus placebo median (Q1, Q3)	p Value
Stage N1, %	5.674 (0.945, 15.733)	3.784 (0.219, 14.545)	−1.37 (−2.43, 0.17)	0.014	4.681 (0.789, 11.364)	−1.28 (−2.84, 0.03)	0.001
Stage N3, %	16.968 (0.000, 39.365)	17.915 (0.000, 34.308)	−0.59 (−2.99, 1.87)	0.475	18.497 (0.173, 35.547)	1.00 (−2.18, 5.18)	0.309
	LS mean (SE)	LS mean (SE)	Diff. vs. placebo LS mean (95% CI)	p Value	LS mean (SE)	Diff. vs. placebo LS mean (95% CI)	p Value
Stage N2, %	60.00 (1.169)	65.17 (1.128)	5.17 (2.73, 7.61)	<0.001	66.00 (1.154)	6.01 (3.57, 8.45)	<0.001
Stage R, %	16.15 (0.782)	12.61 (0.753)	−3.54 (−5.28, −1.80)	<0.001	10.70 (0.772)	−5.45 (−7.20, −3.71)	<0.001

Note: Stages N1 and N3 are presented as median (range) or median difference (Q1 − Q3 difference), with a statistical comparison to placebo using a Wilcoxon signed-rank test on the within-participant differences. Stage N2 and stage R least-squares (LS) means and p values were calculated from a mixed model for repeated measures. p Values are not adjusted for multiplicity.

Abbreviation: LS Mean, least-squares mean.

TABLE 4 Subjective efficacy measures

Measure	Placebo (n = 41)	Zuranolone 30 mg (n = 44)			Zuranolone 45 mg (n = 42)		
	Median (range)	Median (range)	Diff. vs. placebo median (Q1, Q3)	p Value	Median (range)	Diff. vs. placebo median (Q1, Q3)	p Value
sWASO (min)	20.0 (0, 300)	10.0 (0, 120)	−10.0 (−40.0, 0.0)	<0.001	5.0 (0, 300)	−10.0 (−40.0, −5.0)	<0.001
sTST (min)	424.8 (60, 540)	450.0 (40, 555)	11.7 (−4.8, 65.1)	0.026	465.0 (0, 510)	15.0 (0.0, 60.0)	0.001
sSL (min)	15.0 (4, 400)	15.0 (2, 240)	0.0 (−5.0, 0.0)	0.288	10.0 (1, 60)	−5.0 (−10.0, 0.0)	<0.001
sSQ	8.0 (1, 10)	8.0 (5, 10)	1.0 (0.0, 2.0)	<0.001	9.0 (6, 10)	1.0 (0.0, 3.0)	<0.001

Note: Subjective measures are presented as median (range) or median difference (Q1 − Q3 difference), and the statistical comparison to placebo used the Wilcoxon signed-rank test on the within-participant differences. p Values are not adjusted for multiplicity.

Abbreviations: sSL, subjective sleep latency; sSQ, subjective sleep quality; sWASO, subjective wakefulness after sleep onset; sTST, subjective total sleep time.

TABLE 5 Treatment-emergent adverse events in the study

	Placebo (n = 41)	Zuranolone 30 mg (n = 44)	Zuranolone 45 mg (n = 42)
Overall summary			
Any AE	4 (9.8)	5 (11.4)	2 (4.8)
Severe AE	0	0	0
Serious AE	0	0	0
TEAEs ≥ 2 in participants			
Fatigue	0	2 (4.5)	1 (2.4)
Headache	2 (4.9)	1 (2.3)	1 (2.4)

Note: TEAEs occurring in two or more participants in any treatment period are listed as n (%).
Abbreviations: AE, adverse events; TEAE, treatment-emergent adverse events.

total time spent in REM sleep was not different between either dose of zuranolone and placebo, the fraction of overall time spent in REM was reduced. The expansion of time spent in N2 NREM sleep also likely accounts for the observed increase in latency to REM sleep. The current results are most consistent with an expansion of time spent in N2 NREM sleep and therefore TST and decreased WASO occurring in the first three quarters of the night, without a significant change in REM sleep. This interpretation is consistent with the effects of the endogenous neuroactive steroids allopregnanolone and 3α, 5α-THDOC on rodent sleep, where sleep time and NREM significantly increased without impacting REM sleep (Müller-Preuss et al., 2002). More definitive information will await studies in insomnia populations.

Zuranolone is currently in development for the treatment of MDD. Insomnia and MDD are often comorbid, with up to 60% of MDD patients experiencing insomnia (Ford & Kamerow, 1989; Ohayon, 2002; Taylor et al., 2005; Weissman et al., 1996). In a pivotal Phase 2 study of zuranolone in participants with MDD, in addition to achieving the primary endpoint of a statistically significant reduction in the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score at Day 15 versus placebo (Gunduz-Bruce et al., 2019), patients who received zuranolone exhibited significant improvements versus placebo in all three HAMD-17 insomnia items. This included insomnia early (initiation of sleep), insomnia middle (sleep maintenance), and insomnia late (terminal insomnia), at Day 15 (LS means in change from baseline: insomnia early = −1.2 [$p < 0.001$], insomnia middle = −0.7 [$p < 0.001$], and insomnia late = −0.4 [$p = 0.015$] favoring zuranolone compared to placebo). These data are consistent with the current study and further suggest that zuranolone may provide potential additional benefit in patients with comorbid MDD and insomnia.

Overall, there were no clinically significant differences in TEAE frequency among the three treatment groups. Observed TEAEs were mild and consistent with the pharmacology of zuranolone and prior studies of zuranolone (Clayton, 2020; Deligiannidis et al., 2021; Gunduz-Bruce et al., 2019; Hoffmann et al., 2019). No new safety concerns were identified during the trial. Zuranolone 30- and 45-mg doses did not produce significant next-day effects on sleepiness or psychomotor performance; however, KSS results showed a slight trend towards increased signs of sleepiness at the post-PSG assessment in the zuranolone 45-mg group. Full safety and next day effect conclusions are limited by the small size of the study and require further evaluation.

4.1 | Limitations

This study has several limitations, including a relatively small sample of healthy participants, without a sleep disorder diagnosis and sufficient powering for only the primary (PSG) outcome (i.e., SE). Furthermore, the study relied on self-report for sleep diaries between initial screenings through the end of study. In addition, the analysis included no adjustment for multiplicity, which could increase the likelihood of type 1 errors. The study also examined a single night of dosing, so the impact of multiple days of dosing with zuranolone is unclear. Finally, the ability to compare zuranolone to other drugs in terms of efficacy and safety is limited due to the use of placebo as a comparator.

4.2 | Conclusions

Overall, the administration of zuranolone in the 5-h phase advance model of transient insomnia used in this study was associated with improvements in multiple aspects of sleep. These results support the further examination of zuranolone in the treatment of insomnia disorder alone as well as with comorbid MDD.

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CONFLICT OF INTEREST

Amy Bullock, Handan Gunduz-Bruce, Min QinQ, Haihong Li, Abdul J. Sankoh, Christopher SilberS, Stephen J. Kanes, Jeffrey Jonas, and James Doherty are employees of Sage Therapeutics with stock/stock options. Gary K. Zammit is an employee and shareholder of Clinilabs, Inc., and has ownership interests in Home Sleep and Respiratory Care, Sleep Disorders Institute, and Nationwide Sleep Testing. He has served as a consultant for Eisai, Idorsia, Jazz, Purdue, and Takeda.

DATA AVAILABILITY STATEMENT

Research data is not shared.

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REFERENCES

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed.). American Psychiatric Association.

Belelli, D., Peden, D. R., Rosahl, T. W., Wafford, K. A., & Lambert, J. J. (2005). Extrasynaptic GABAA receptors of thalamocortical neurons: A molecular target for hypnotics. *Journal of Neuroscience*, *25*(50), 11513–11520. https://doi.org/10.1523/JNEUROSCI.2679-05.2005

Bonnet, M. H., & Arand, D. L. (2003). Situational insomnia: Consistency, predictors, and outcomes. *Sleep*, *26*(8), 1029–1036.

Brickley, S. G., Cull-Candy, S. G., & Farrant, M. (1999). Single-channel properties of synaptic and extrasynaptic GABAA receptors suggest differential targeting of receptor subtypes. *Journal of Neuroscience*, *19*(8), 2960–2973. https://doi.org/10.1523/jneurosci.19-08-02960.1999

Chung, S., Weber, F., Zhong, P., Tan, C. L., Nguyen, T., Beier, K. T., Hörmann, N., Chang, W.-C., Zhang, Z., Do, J. P., Yao, S., Krashes, M. J., Tasic, B., Cetin, A., Zeng, H., Knight, Z. A., Luo, L., & Dan, Y. (2017). Identification of preoptic sleep neurons using retrograde labelling and gene profiling. *Nature*, *545*(7655), 477–481. https://doi.org/10.1038/nature22350

Clayton, A. H. (2020). A phase 3, multicenter, double-blind, randomized, placebo-controlled study evaluating the efficacy of zuranolone in the treatment of adult patients with major depressive disorder. *Presented at the Society of Biological Psychiatry Annual Meeting*.

Deligiannidis, K. M., Meltzer-Brody, S., Gunduz-Bruce, H., Doherty, J., Jonas, J., Li, S., Sankoh, A. J., Silber, C., Campbell, A. D., Werneburg, B., Kanes, S. J., & Lasser, R. (2021). Effect of Zuranolone vs Placebo in postpartum depression: A randomized clinical trial. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2021.1559

Finan, P. H., Quartana, P. J., & Smith, M. T. (2015). The effects of sleep continuity disruption on positive mood and sleep architecture in healthy adults. *Sleep*, *38*(11), 1735–1742. https://doi.org/10.5665/sleep.5154

Ford, D. E., & Kamerow, D. B. (1989). Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *Journal of the American Medical Association*, *262*(11), 1479–1484. https://doi.org/10.1001/jama.262.11.1479

Furey, S. A., Hull, S. G., Leibowitz, M. T., Jayawardena, S., & Roth, T. (2014). A randomized, double-blind, placebo-controlled, multicenter, 28-day, polysomnographic study of gabapentin in transient insomnia induced by sleep phase advance. *Journal of Clinical Sleep Medicine*, *10*(10), 1101–1109. https://doi.org/10.5664/jcsm.4110

Gunduz-Bruce, H., Silber, C., Kaul, I., Rothschild, A. J., Riesenberg, R., Sankoh, A. J., Li, H., Lasser, R., Zorumski, C. F., Rubinow, D. R., Paul, S. M., Jonas, J., Doherty, J. J., & Kanes, S. J. (2019). Trial of SAGE-217 in patients with major depressive disorder. *New England Journal of Medicine*, *381*(10), 903–911. https://doi.org/10.1056/NEJMoa1815981

Hoffmann, E., Nomikos, G. G., Kaul, I., Raines, S., Wald, J., Bullock, A., Sankoh, A. J., Doherty, J., Kanes, S. J., & Colquhoun, H. (2019). SAGE-217, a novel $GABA_A$ receptor positive allosteric modulator: Clinical pharmacology and tolerability in randomized phase I dose-finding studies. *Clinical Pharmacokinetics*, *59*, 111–120. https://doi.org/10.1007/s40262-019-00801-0

Horoszok, L., Baleeiro, T., D'Aniello, F., Gropper, S., Santos, B., Guglietta, A., & Roth, T. (2014). A single-dose, randomized, double-blind, double dummy, placebo and positive-controlled, five-way cross-over study to assess the pharmacodynamic effects of lorediplon in a phase advance model of insomnia in healthy Caucasian adult male subjects. *Human Psychopharmacology*, *29*(3), 266–273. https://doi.org/10.1002/hup.2395

Hosie, A. M., Wilkins, M. E., da Silva, H. M. A., & Smart, T. G. (2006). Endogenous neurosteroids regulate GABAA receptors through two discrete transmembrane sites. *Nature*, *444*(7118), 486–489. https://doi.org/10.1038/nature05324

Kanno, O., Watanabe, H., & Kazamatsuri, H. (1993). Effects of zopiclone, flunitrazepam, triazolam and levomepromazine on the transient change in sleep-wake schedule: Polygraphic study, and the evaluation of sleep and daytime condition. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *17*(2), 229–239. https://doi.org/10.1016/0278-5846(93)90044-s

Laverty, D., Thomas, P., Field, M., Andersen, O. J., Gold, M. G., Biggin, P. C., Gielen, M., & Smart, T. G. (2017). Crystal structures of a GABA A-receptor chimera reveal new endogenous neurosteroid-binding sites. *Nature Structural & Molecular Biology*, *24*(11), 977–985. https://doi.org/10.1038/nsmb.3477

LeBlanc, M., Mérette, C., Savard, J., Ivers, H., Baillargeon, L., & Morin, C. M. (2009). Incidence and risk factors of insomnia in a population-based sample. *Sleep*, *32*(8), 1027–1037. https://doi.org/10.1093/sleep/32.8.1027

Lin, J. S., Sakai, K., Vanni-Mercier, G., & Jouvet, M. (1989). A critical role of the posterior hypothalamus in the mechanisms of wakefulness determined by microinjection of muscimol in freely moving cats. *Brain Research*, *479*(2), 225–240. https://doi.org/10.1016/0006-8993(89)91623-5

Löscher, W., & Rogawski, M. A. (2012). How theories evolved concerning the mechanism of action of barbiturates. *Epilepsia*, *53*(s8), 12–25. https://doi.org/10.1111/epi.12025

Martinez Botella, G., Salituro, F. G., Harrison, B. L., Beresis, R. T., Bai, Z., Blanco, M.-J., Belfort, G. M., Dai, J., Loya, C. M., Ackley, M. A., Althaus, A. L., Grossman, S. J., Hoffmann, E., Doherty, J. J., & Robichaud, A. J. (2017). Neuroactive steroids. 2. 3α-Hydroxy-3β-methyl-21-(4-cyano-1 H-pyrazol-1′-yl)-19-nor-5β-pregnan-20-one (SAGE- 217): A clinical next generation neuroactive steroid positive allosteric modulator of the $(\gamma\text{-aminobutyric acid})_A$ receptor. *Journal of Medicinal Chemistry*, *60*(18), 7810–7819. https://doi.org/10.1021/acs.jmedchem.7b00846

Müller-Preuss, P., Rupprecht, R., & Lancel, M. (2002). The effects of the neuroactive steroid 3 alpha,5 alpha-THDOC on sleep in the rat. *Neuroreport*, *13*(4), 487–490. https://doi.org/10.1097/00001756-200203250-00026

National Institutes of Health. (2005). National Institutes of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults, June 13-15, 2005. *Sleep*, *28*(9), 1049–1057. https://doi.org/10.1093/sleep/28.9.1049

National Sleep Foundation. (2002). *2002 "Sleep in America" Poll*. https://www.sleepfoundation.org/sites/default/files/inline-files/2002SleepInAmericaPoll.pdf

National Sleep Foundation. (2005). *2005 "Sleep in America" Poll*. https://www.sleepfoundation.org/sites/default/files/inline-files/2005_summary_of_findings.pdf

Nitz, D., & Siegel, J. M. (1996). GABA release in posterior hypothalamus across sleep-wake cycle. *American Journal of Physiology*, *271*(6 Pt 2), R1707–R1712. https://doi.org/10.1152/ajpregu.1996.271.6.R1707

Nofzinger, E. A., Buysse, D. J., Germain, A., Price, J. C., Miewald, J. M., & Kupfer, D. J. (2004). Functional neuroimaging evidence for hyperarousal in insomnia. *American Journal of Psychiatry*, *161*(11), 2126–2128. https://doi.org/10.1176/appi.ajp.161.11.2126

Ohayon, M. M. (2002). Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Medicine Reviews*, *6*(2), 97–111. https://doi.org/10.1053/smrv.2002.0186

Ohayon, M. M. (2009). Difficulty in resuming or inability to resume sleep and the links to daytime impairment: Definition, prevalence and comorbidity. *Journal of Psychiatric Research*, *43*(10), 934–940. https://doi.org/10.1016/j.jpsychires.2009.01.011

Ohayon, M. M., Krystal, A., Roehrs, T. A., Roth, T., & Vitiello, M. V. (2010). Using difficulty resuming sleep to define nocturnal awakenings. *Sleep Medicine*, *11*(3), 236–241. https://doi.org/10.1016/j.sleep.2009.11.004

Ohayon, M. M., Shapiro, C. M., & Kennedy, S. H. (2000). Differentiating DSM-IV anxiety and depressive disorders in the general population: Comorbidity and treatment consequences. *Canadian Journal of Psychiatry*, *45*(2), 166–172. https://doi.org/10.1177/070674370004500207

Paiva, T., Gaspar, T., & Matos, M. G. (2015). Sleep deprivation in adolescents: Correlations with health complaints and health-related quality of life. *Sleep Medicine*, *16*(4), 521–527. https://doi.org/10.1016/j.sleep.2014.10.010

Parthasarathy, S., Vasquez, M. M., Halonen, M., Bootzin, R., Quan, S. F., Martinez, F. D., & Guerra, S. (2015). Persistent insomnia is associated with mortality risk. *American Journal of Medicine*, *128*(3), 268–275.e2. https://doi.org/10.1016/j.amjmed.2014.10.015

Perlis, M., Shaw, P. J., Cano, G., & Espie, C. A. (2011). Models of insomnia. *Principles and Practice of Sleep Medicine*, *5*, 850–865.

Rosenberg, R. P., Hull, S. G., Lankford, D. A., Mayleben, D. W., Seiden, D. J., Furey, S. A., Jayawardena, S., & Roth, T. (2014). A randomized, double-blind, single-dose, placebo-controlled, multicenter, polysomnographic study of gabapentin in transient insomnia induced by sleep phase advance. *Journal of Clinical Sleep Medicine*, *10*(10), 1093–1100. https://doi.org/10.5664/jcsm.4108

Roth, T., Heith Durrence, H., Jochelson, P., Peterson, G., Ludington, E., Rogowski, R., Scharf, M., & Lankford, A. (2010). Efficacy and safety of doxepin 6 mg in a model of transient insomnia. *Sleep Medicine*, *11*(9), 843–847. https://doi.org/10.1016/j.sleep.2010.07.006

Roth, T., Roehrs, T., & Vogel, G. (1995). Zolpidem in the treatment of transient insomnia: A double-blind, randomized comparison with placebo. *Sleep*, *18*(4), 246–251. https://doi.org/10.1093/sleep/18.4.246

Scalo, J., Desai, P., & Rascati, K. (2014). Insomnia, hypnotic use, and health-related quality of life in a nationally representative sample. *Quality of Life Research*, *24*(5), 1223–1233. https://doi.org/10.1007/s11136-014-0842-1

Sherin, J. E., Elmquist, J. K., Torrealba, F., & Saper, C. B. (1998). Innervation of histaminergic tuberomammillary neurons by GABAergic and galaninergic neurons in the ventrolateral preoptic nucleus of the rat. *Journal of Neuroscience*, *18*(12), 4705–4721. https://doi.org/10.1523/jneurosci.18-12-04705.1998

Staner, L., Eriksson, M., Cornette, F., Santoro, F., Muscat, N., Luthinger, R., & Roth, T. (2009). Sublingual zolpidem is more effective than oral zolpidem in initiating early onset of sleep in the post-nap model of transient insomnia: A polysomnographic study. *Sleep Medicine*, *10*(6), 616–620. https://doi.org/10.1016/j.sleep.2008.06.008

Stell, B. M., & Mody, I. (2002). Receptors with different affinities mediate phasic and tonic GABA(A) conductances in hippocampal neurons. *Journal of Neuroscience*, *22*(10), RC223. https://doi.org/10.1523/jneurosci.22-10-j0003.2002

Stewart, R., Besset, A., Bebbington, P., Brugha, T., Lindesay, J., Jenkins, R., Singleton, N., & Meltzer, H. (2006). Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years. *Sleep*, *29*(11), 1391–1397. https://doi.org/10.1093/sleep/29.11.1391

Stone, B. M., Turner, C., Mills, S. L., Paty, I., Patat, A., Darwish, M., & Danjou, P. (2002). Noise-induced sleep maintenance insomnia: Hypnotic and residual effects of zaleplon. *British Journal of Clinical Pharmacology*, *53*(2), 196–202. https://doi.org/10.1046/j.-5251.2001.01520.x

Svetnik, V., Ferri, R., Ray, S., Ma, J., Walsh, J. K., Snyder, E., Ebert, B., & Deacon, S. (2010). Alterations in cyclic alternating pattern associated with phase advanced sleep are differentially modulated by gaboxadol and zolpidem. *Sleep*, *33*(11), 1562–1570. https://doi.org/10.1093/sleep/33.11.1562

Taylor, D. J., Lichstein, K. L., Durrence, H. H., Reidel, B. W., & Bush, A. J. (2005). Epidemiology of insomnia, depression, and anxiety. *Sleep*, *28*(11), 1457–1464. https://doi.org/10.1093/sleep/28.11.1457

Uygun, D. S., Ye, Z., Zecharia, A. Y., Harding, E. C., Yu, X., Yustos, R., Vyssotski, A. L., Brickley, S. G., Franks, N. P., & Wisden, W. (2016). Bottom-up versus top-down induction of sleep by zolpidem acting on histaminergic and neocortex neurons. *Journal of Neuroscience*, *36*(44), 11171–11184. https://doi.org/10.1523/jneurosci.3714-15.2016

Walsh, J. K., Deacon, S., Dijk, D. J., & Lundahl, J. (2007). The selective extrasynaptic GABAA agonist, gaboxadol, improves traditional hypnotic efficacy measures and enhances slow wave activity in a model of transient insomnia. *Sleep*, *30*(5), 593–602. https://doi.org/10.1093/sleep/30.5.593

Walsh, J. K., Schweitzer, P. K., Sugerman, J. L., & Muehlbach, M. J. (1990). Transient insomnia associated with a 3-hour phase advance of sleep time and treatment with zolpidem. *Journal of Clinical Psychopharmacology*, *10*(3), 184–189.

Weissman, M. M., Bland, R. C., Canino, G. J., Faravelli, C., Greenwald, S., Hwu, H. G., Joyce, P. R., Karam, E. G., Lee, C. K., Lellouch, J., Lépine, J. P., Newman, S. C., Rubio-Stipec, M., Wells, J. E., Wickramaratne, P. J., Wittchen, H., & Yeh, E. K. (1996). Cross-national epidemiology of major depression and bipolar disorder. *Journal of the American Medical Association*, *276*(4), 293–299.

Wisden, W., Yu, X., & Franks, N. P. (2017). GABA receptors and the pharmacology of sleep. *Handbook of Experimental Pharmacology*, *253*, 279–304. https://doi.org/10.1007/164_2017_56

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