Original Article

Effects of Acute Aerobic Exercise *Versus* Acute Zolpidem Intake on Sleep in Individuals with Chronic Insomnia

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Sleep Sci

Abstract

Introduction Sleeping pills are assumed to be the most efficacious means of treating acute insomnia, but their use has associated risks. Exercise could provide a healthy alternative treatment for insomnia, particularly if it could be shown to have comparable efficacy to sleeping pills.

Objective The purpose of this study was to compare the effects of acute exercise *versus* zolpidem on chronic insomnia.

Methods Seventeen participants with chronic insomnia (recruited from advertisements) participated in a parallel randomized controlled trial (exercise, $n = 9$; zolpidem, $n = 8$). Participants in the exercise treatment performed treadmill exercise for 50 minutes, at 50% of heart rate reserve, between 11 AM and 2 PM. Participants in the zolpidem treatment received a 10 mg dose of zolpidem immediately before bedtime. Following baseline and following the treatment, sleep measures included sleep diary, polysomnography, and actigraphy. Treatments were compared with non-inferiority analysis, ANOVA, and effect sizes.

Results Non-inferiority of exercise relative to zolpidem was observed for polysomnographic measurement of sleep latency. For all other comparisons, the non-inferiority was inconclusive. Significant treatment-by-time interactions were observed for N3 sleep ($p = 0.04$) and REM sleep ($p = 0.03$). No other significant treatment-by-time effects were observed. Subjective sleep duration and sleep efficiency, and polysomnographic measurement of sleep efficiency were significantly increased after zolpidem and exercise. The effect size between groups was small for these variables.

Conclusion Exercise impacted sleep in a similar way to zolpidem in participants with chronic insomnia. Considering the far superior health benefits of exercise, further research addressing this question is warranted.

Keywords
► insomnia
► sleep initiation and maintenance disorders
► exercise
► complementary therapies
► hypnotics and sedatives

Introduction

Chronic insomnia is characterized by nighttime and associated daytime symptoms for at least 3 months, and in acute or short-term insomnia the sleep disturbance and daytime symptoms have been present for < 3 months.[1] Chronic insomnia has a worldwide prevalence of 9 to 17%.[2] Hyperarousal during sleep and wakefulness have been observed in patients with chronic insomnia,[3] and 24-hour increased cortisol have been suggested.[4] Insomnia is associated with an increased risk of mortality, as well as hypertension, cardiovascular disease, heart failure, and depression.[5–8]

Insomnia is commonly treated with sleeping pills. However, because chronic sleeping pill use is associated with increased mortality,[9] tolerance, and reduced efficacy,[10] sleeping pills are generally not recommended for chronic use.

Nonetheless, sleeping pills are generally regarded as the most effective treatment for acute or short-term management of insomnia.[11] However, hazardous side effects of a single dose or short-term use of sleeping pills can include prolonged sedation, "sleep-driving," risk of falls, and impaired daytime performance.[12] Thus, there is a need to explore whether other treatments might have similar benefits as sleeping pills for the acute treatment of insomnia.

A potentially attractive alternative to sleeping pills is moderate-intensity aerobic exercise, which contrasts starkly with sleeping pills because of the well-known health benefits of both acute exercise (a single bout)[13,14] and chronic exercise training (16 weeks – 6 months).[15,16]

Multiple studies have found significant benefits of acute exercise on sleep in individuals with sleep impairment and chronic insomnia.[13,14,17,18] For example, Passos et al.[13] reported that acute moderate-intensity treadmill exercise for 50 minutes significantly improved sleep diary measures of total sleep time (TST) and sleep latency, sleep efficiency (SE) and polysomnographic (PSG) measures of SE, TST, sleep latency and total wake time. Moreover, Chen et al.[18] demonstrated a reduction in actigraphic sleep latency and an increase in SE after an acute bout of light-intensity walking. A single bout of exercise can also elicit reductions in anxiety,[19] depression,[20] and blood pressure,[21] and in animal models can reduce susceptibility to a subsequent cardiovascular event.[22]

Some evidence has indicated that chronic aerobic exercise can elicit a decrease in levels of morning cortisol,[23] and that there is a correlation between a reduction in morning cortisol and a reduction in the insomnia severity after chronic exercise, in patients with chronic insomnia.[24] Demonstrating that acute exercise is not appreciably inferior to sleeping pills for promoting sleep could help reinforce the chronic treatment of insomnia with exercise and its overwhelming health benefits. Conversely, such evidence could help dissuade the use of sleeping pills and its resulting risks.

This study aimed to compare the effects of acute exercise and zolpidem (10 mg), one of the most widely used sleeping pills, for improving sleep in individuals with chronic insomnia.

Materials and Methods

Ethical approval for all experimental measures was granted by the University Human Research Ethics Committee (Universidade Federal de Goiás, #2.835.224) and conformed to principles outlined in the Declaration of Helsinki. This study is registered at www.clinicaltrials.gov (ID: NCT03160404).

Participants and Screening

Participants were recruited through newspaper advertisements and online media (from April 2018 to December 2019). Prospective participants contacted the researchers and were initially screened with a brief phone interview. Participants who met the initial study criteria and remained interested were invited to the research laboratory. Following a more comprehensive description of the study, they signed written informed consent, and underwent further extensive screening, including a meeting with the sleep doctor/neurologist (for the clinical diagnosis of chronic insomnia), physical evaluation (the demographic characteristic of participants, age, body mass, stature, and %fat). The participants also filled out some questionaries (Insomnia Severity Index – ISI and BECK depression inventory) used to describe the sample and they were submitted to a treadmill test with a cardiologist.

The inclusion criteria included: (a) age between 30 and 60 years old; (b) clinical diagnosis of chronic insomnia based on DSM-V[25]; (c) insomnia complaints at least 3 times/week, for at least 3 months; (d) being physically inactive (exercise less than twice a week). The exclusion criteria included: (a) evidence that insomnia was directly related to medical conditions or side effects of drugs; (b) obstructive sleep apnea (AHI> 5); (c) periodic limb movement index > 15; (c) abnormalities in the EKG (electrocardiogram) during the treadmill exercise test; d) use of β-blockers; (e) uncontrolled clinical diseases (diabetes, high blood pressure, cardiovascular, neurological or renal diseases); (f) history of abuse of alcohol or psychoactive substances, except tobacco; (g) Beck Depression Inventory score> 20 or diagnosis of major depression; (h) being a shift workers; (i) BMI> 30; (j) use of pharmacological therapy for insomnia, anxiety or depression that could not be stopped.

Participants using sleeping drugs no more than twice weekly were enrolled after they withdrew from the medications for at least two weeks, as described by Morin et al.[26] A sleep doctor/neurologist conducted the withdrawal from the sleeping pills. After medical screening, the participants used a half dose of the drug for 5 days, and in the next week, they used a half dose every other day. In the next week, no drugs were used. We delayed the start of the study by more than one week to accomplish this tapering.

The participants were randomly assigned to one of two treatments (exercise or zolpidem). Simple randomization (1:1 ratio) was performed using opaque and sealed envelopes, identified as exercise or zolpidem treatment.

Research Design

This was a clinical study that involved two days of assessment: baseline and the experimental treatment day (a single bout of exercise or zolpidem). At baseline, participants

arrived at the sleep laboratory at 9 PM and placed one actigraph device on his/her wrist. Thirty minutes before bedtime, participants were prepared for polysomnographic recording, and at habitual sleep time, the lights-out indicated the beginning of baseline polysomnographic recording. On the following morning, a fasting blood sample was collected (at $08:00 \pm 1$ hour), and the participants filled out a sleep diary. The actigraphy device was removed, On the experimental day, participants either performed the exercise or zolpidem treatment (described below), and the procedures for actigraphic and polysomnographic recording, cortisol collection, and the sleep diary were duplicated.

Moderate-intensity Aerobic Exercise Treatment

The exercise session (single bout) was performed on a treadmill *Movement*® (BR)-LX 160, for 50 minutes, at an intensity of 50% of heart rate reserve (HRR) ± 5 bpm, between 11 AM and 2 PM The session was preceded by stretching of the upper and lower limbs and five minutes of warm-up and followed by five minutes of active recovery. HRR was calculated by the formula ([**(max HR – resting HR)** $\times$ **%Intensity]** + **resting HR).** HRmax was estimated calculated by the traditional formula "220 minus age" and resting HR was registered by a Polar FT1 (in the medical screening).

Zolpidem

Participants in this treatment received a 10 mg tablet of Zolpidem (Stilnox®, Sanofi-Aventis), single dosage. Participants were instructed to consume the tablet immediately before bedtime. Zolpidem is a non-benzodiazepine agonist at the subtypes of benzodiazepine receptors that has a rapid onset of action and a short half-life (mean 2.5 hours).

Instruments

Sleep Diary

The sleep diary used in this study followed the recommendation of The Consensus Sleep Diary.[27] The following variables were derived from the sleep diary: sleep latency, wake time after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE, ratio between total sleep time and total time in bed multiplied by 100), and sleep debt. Sleep debt was calculated by the difference between the hours obtained in the first question of the sleep diary "How many hours do you need sleep to be restored in the following morning? and the mean of TST obtained in the sleep diary."

Polysomnography (PSG)

PSG was performed using the ICELERA (*i blue*, version 1.1.39) device at f 30-second epochs classified as awake, sleep stages N1, N2, and N3 (non-rapid eye movement–NREM), and REM (rapid eye movement) sleep according to the criteria standardized by Iber et al.[28] Four EEG leads (C3-A2, C4-A1, Fz-A1, and O1-A1), 2 EOG channels (C3), 2 EMG channels (submental and legs), and1 ECG lead (modified D2) were recorded. Sleep variables analyzed were TST, SE, sleep latency, REM latency (LREM), wake time after sleep onset (WASO), arousals, apnea-hypopnea index (AHI), periodic leg movements (PLM), and percentage of sleep stages. The analysis of the events in the polysomnography was performed by two investigators who used international criteria and were blind to treatment.

Actigraphy

Actigraphy was recorded using the Micro MotionLogger® model (Ambulatory Monitoring, Inc., USA). It is a device like a wristwatch, which allows determining the pattern of the wake-sleep cycle by recording motor activity resulting from body movements. The Software package Action4 was used for the research data analysis. These measures included TST, SE, WASO, sleep latency, and awakenings. Actigraphy have shown correspondence with polysomnographic has measures of sleep in normal sleepers[29] and patients with insomnia.[30]

Morning Cortisol Level

A sample blood was collected at $08:00 \pm 1$ hour, at the Sleep Clinic following the polysomnography, before the participants ate, drank, or brushed their teeth. Serum cortisol was analyzed by chemiluminescence.

Statistical Analysis

The non-inferiority margin for the mean difference in the sleep variables was evaluated between the two treatments. Non-inferiority was defined *a priori* as a baseline to treatment increases in a sleep diary, actigraphy and PSG estimates of TST that were less than 20 minutes greater following zolpidem versus exercise; a baseline to treatment decreases in sleep latency that was < 10 minutes greater following zolpidem versus exercise; a baseline to treatment increase in SE that was $< 1.5\%$ greater following zolpidem versus exercise; and a baseline to treatment decrease in WASO that was < 20 minute greater following zolpidem vs exercise.

Treatment by time (baseline and post-treatment) ANOVAs were performed for the primary outcome variable (total sleep time evaluated by sleep diary) and for the secondary outcome variables with Stata version 17.0. One of the assumptions of repeated measure ANOVA is compound symmetric as the within-subject covariance structure. In case of the violation of the assumption, *p*-values from three conservative F-tests, including Hyunh-Feldt, Greenhouse-Geisser, and Box, were considered together to interpret the results (*repeated ()* option in *anova* command in Stata). The results were presented with 95% confidence intervals (C.I.) so that the lower or upper bound could be compared with the predetermined noninferiority margin for each outcome.

Effect sizes for the treatment by time interactions are reported with partial η^2, which is one of the r-family members measuring a proportion of the total variance accounted for by a given factor. In general, an η^2 of 0.01, 0.06, and 0.014 can be considered as small, medium, and large effects, respectively.[31] Data are presented as mean $\pm$ SD. The significance level was at $p < 0.05$.

Results

One hundred and forty-three individuals were interested in participating in the study. Of this total, 131 were excluded by
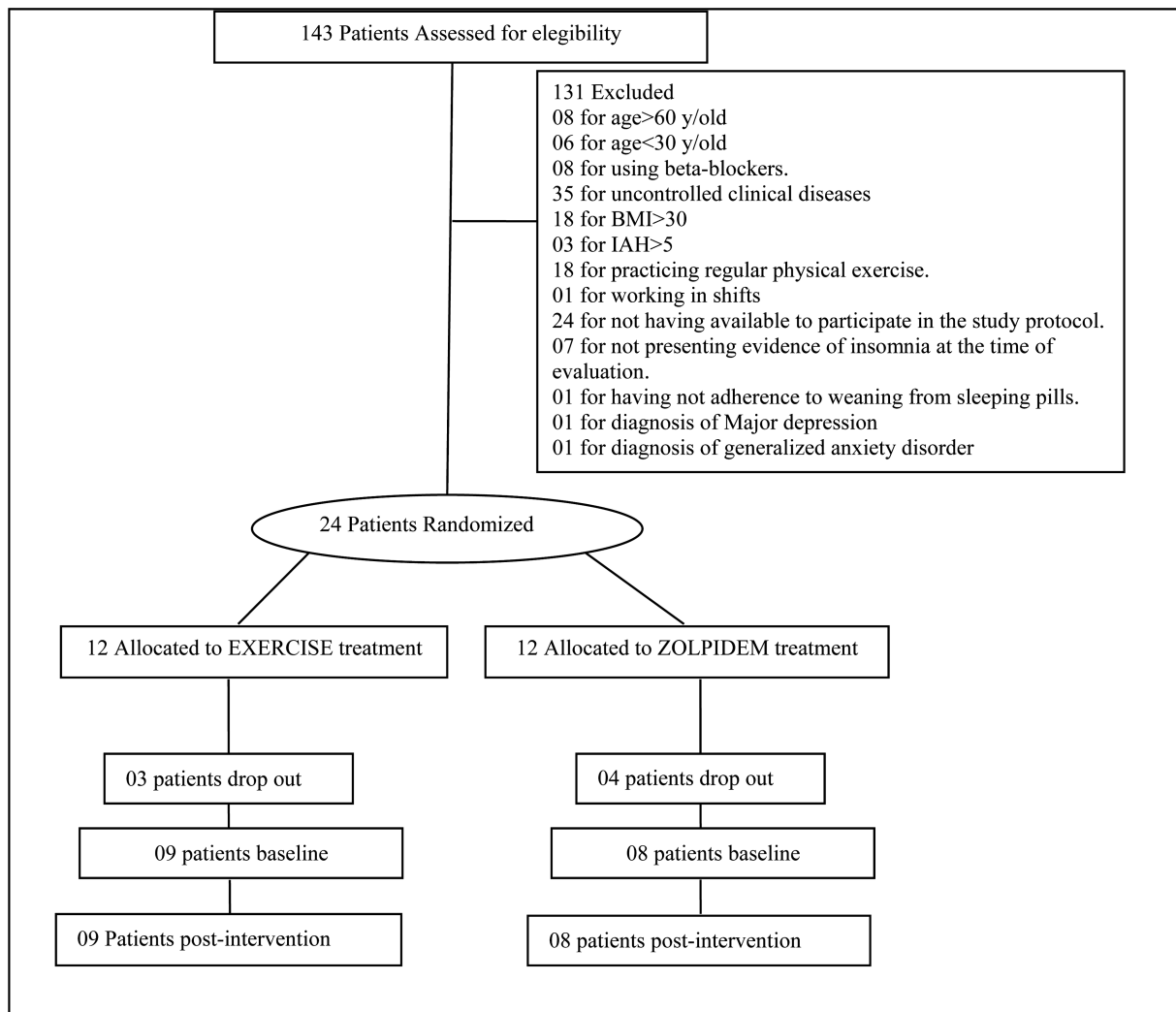
Fig. 1 Participant flowchart.

the inclusion/exclusion criteria of the study, and 24 participants were randomized to the treatments (►**Fig. 1**). Seventeen participants completed the protocol (Exercise, $n = 9$; zolpidem, $n = 8$).

Four participants were using drugs before the study. Two were using zolpidem, one was using quetiapine, and one was clonazepam. One patient using zolpidem was randomized to exercise treatment and the other for zolpidem. The patient using quetiapine was randomized to exercise treatment and

the patient using clonazepam for zolpidem treatment. Only one patient did not accept a stay without drugs to participate in the study and was excluded.

The baseline characteristics of the participants randomized to exercise or zolpidem treatment are shown in ►**Table 1**.

Non-inferiority Results
►**Figs. 2a-2d** shows the non-inferiority results for the sleep diary measures of TST, WASO, SE, and sleep latency,

Table 1 Baseline characteristic of the participants randomized to exercise or zolpidem treatment

	ZOLPIDEM ($n = 8$)	EXERCISE ($n = 9$)
Age (y)	47.3 ± 7.1	43.3 ± 8.7
Body Mass (kg)	68.9 ± 7.7	65.3 ± 9.0
BMI (kg/m^2)	25.3 ± 2.6	24.4 ± 2.2
Fat (%)	34.9 ± 8.1	33.3 ± 6.3
ISI (score)	16.3 ± 3.4	16.3 ± 3.2
BDI (score)	13.0 ± 6.5	12.8 ± 6.6

Abbreviations: BMI, body mass index; BDI, Beck Depression Inventory; ISI, Insomnia Severity Index.
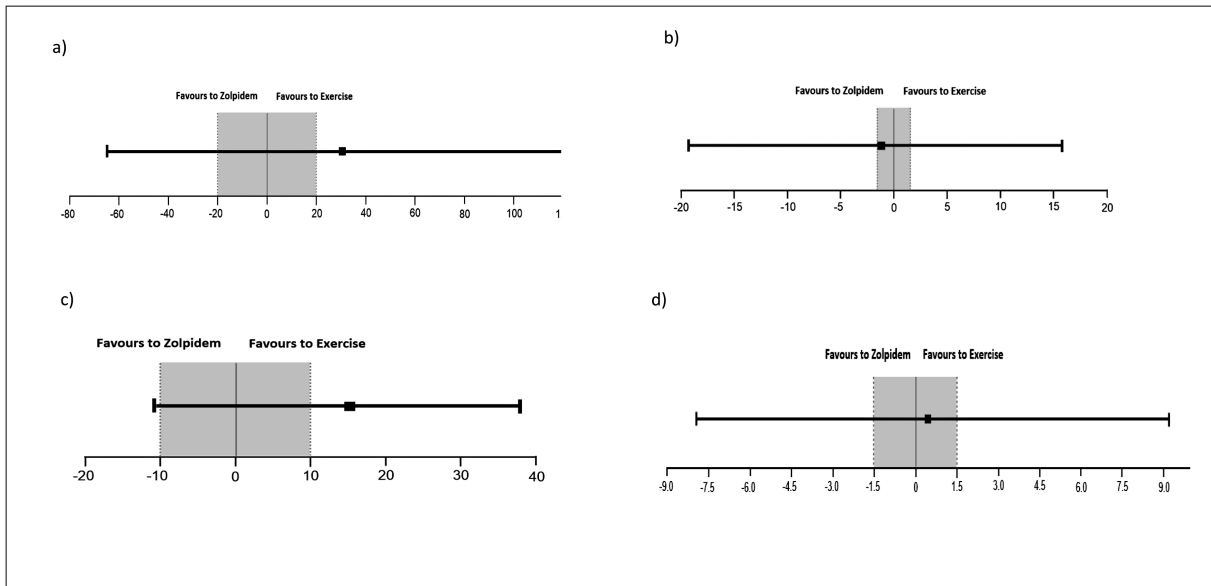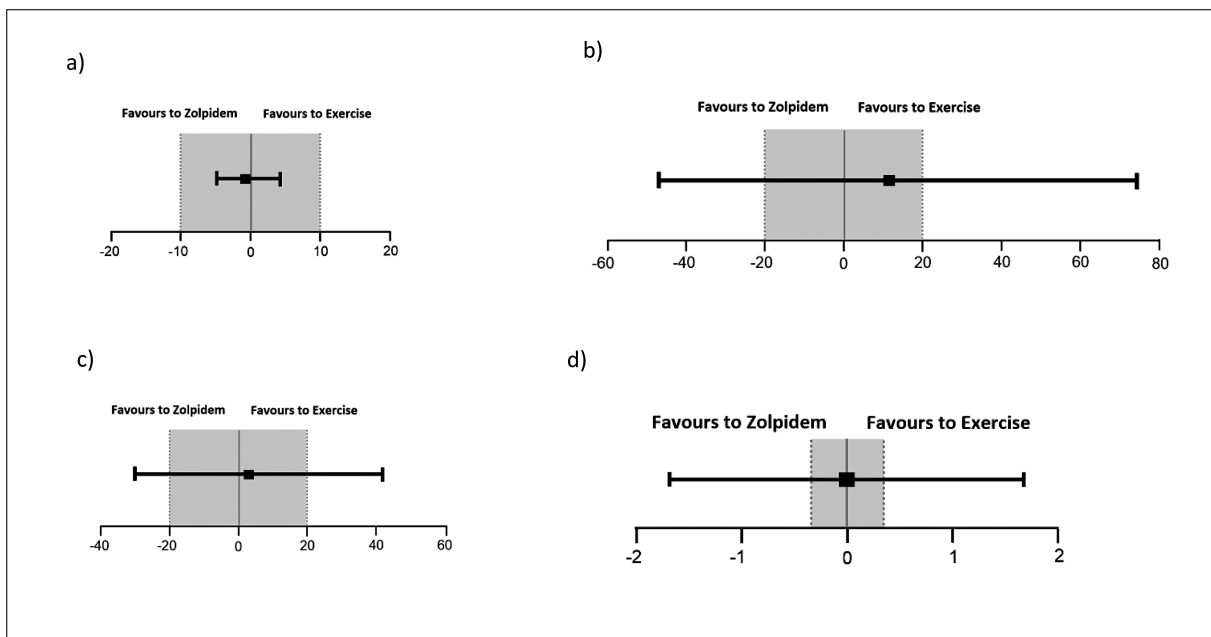
Fig. 2 Sleep Variables evaluated by Sleep Diary. (a) Treatment difference between exercise and zolpidem on the total sleep time. The dotted line (-0.33 to 0.33 hours) indicates the margin of non-inferiority; (b) the treatment difference between exercise and zolpidem on the wake time after sleep onset. The dotted line (-20 to 20 minutes) indicates the margin of non-inferiority; (c) the treatment difference between exercise and zolpidem on sleep efficiency. The dotted line (-1.5 to 1.5%) indicates the margin of non-inferiority; (d) the treatment difference between exercise and zolpidem on the sleep latency. The dotted line (-10 to 10 minutes) indicates the margin of non-inferiority.

respectively. These figures were adapted from the CONSORT statement for non-inferiority trials.[32] For each of these variables, the 95% CI exceeded the *a priori*-defined margins to demonstrate non-inferiority.

►**Fig. 3a** shows the non-inferiority results for PSG-defined sleep latency. Non-inferiority of exercise compared with zolpidem was demonstrated. ►**Figs. 3b-3d** shows the non-

inferiority results for the PSG measures of SE, TST, and WASO, respectively. The 95% CI exceeds the previously defined margins to demonstrate non-inferiority.

►**Figs. 4a-4d** shows inferior results for the actigraphy measures of TST, SE, sleep latency, and WASO, respectively. The 95% CI exceeds the previously defined margins to demonstrate non-inferiority.

Fig. 3 Sleep Variables evaluated by Polysomnography. (a) Treatment difference between exercise and zolpidem on the sleep latency. The dotted line (-10 to 10 minutes) indicates the margin of non-inferiority; (b) Treatment difference between exercise and zolpidem on sleep efficiency. The dotted line (-1.5 to 1.5%) indicates the margin of non-inferiority; (c) the treatment difference between exercise and zolpidem on the total sleep time. The dotted line (-20 to 20 minutes) indicates the margin of non-inferiority; (d) the treatment difference between exercise and zolpidem on the wake time after sleep onset. The dotted line (-20 to 20 minutes) indicates the margin of non-inferiority.
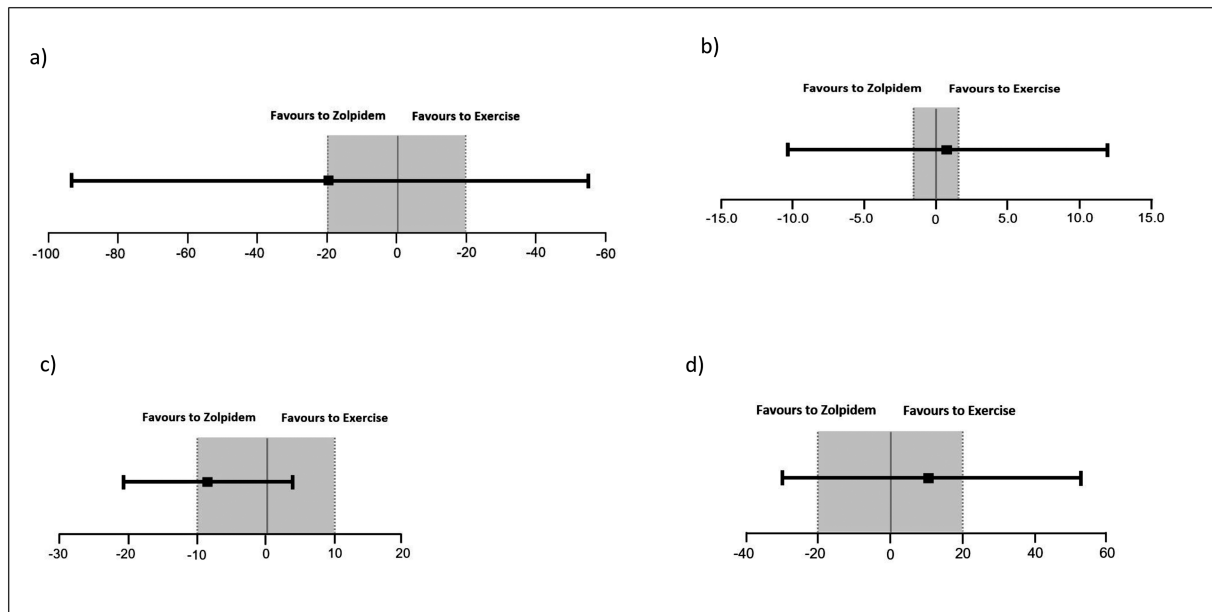
Fig. 4 Sleep Variables evaluated by Actigraphy. (a) Treatment difference between exercise and zolpidem on the total sleep time. The dotted line (-20 to 20 minutes) indicates the margin of non-inferiority. (b) the treatment difference between exercise and zolpidem on the sleep efficiency. The dotted line (-1.5 to 1.5%) indicates the margin of non-inferiority; (c) the treatment difference between exercise and zolpidem on the sleep latency. The dotted line (-10 to 10 minutes) indicates the margin of non-inferiority; (d) the treatment difference between exercise and zolpidem on the wake time after sleep onset. The dotted line (-20 to 20 minutes) indicates the margin of non-inferiority.

ANOVA and Effect Size Results

Sleep diary data are displayed in ►**Table 2**. Sleep diary measures of total sleep time and sleep efficiency increased significantly after both treatments. However, the treatment-by-time effects were not significant for either of these variables. Sleep latency and WASO decreased significantly after zolpidem treatment. However, the treatment by time effects were not significant for either of these variables.

A moderate effect size between treatments was found for the diary measure of sleep latency ($\eta^2 = 0.11$). The reduction in sleep latency was 25.4 ± 29.5 minutes (mean ± S.D) after zolpidem and 11.3 ± 12.7 minutes after exercise. The effect size treatment comparisons for the other sleep variables were all small in magnitude.

►**Table 3** displays the polysomnographic (PSG) data. Significant treatment-by-time interactions were observed for the percentage of N3 sleep ($p = 0.04$) and the percentage of REM sleep ($p = 0.03$). Compared with baseline, zolpidem elicited an increase in N3 sleep ($7.5 \pm 10.7\%$), whereas exercise elicited a small decrease ($-4.4 \pm 10.6\%$). Zolpidem and exercise elicited a small decrease and a small increase in REM sleep, respectively. Sleep efficiency evaluated by polysomnography increased significantly after zolpidem and exercise. A significant increase in REM latency and a significant decrease in WASO were observed only after zolpidem treatment, and a significant increase in total sleep time was observed only after exercise treatment. However, no significant treatment by time effects were observed for these outcomes.

Large between-treatment effect sizes were found for REM latency ($\eta^2 = 0.20$), N3 Sleep ($\eta^2 = 0.26$), and REM sleep ($\eta^2 = 0.27$). REM latency increased by 60.9 ± 76.3 minutes after zolpidem and 2.4 ± 47.7 minutes after exercise. N3 sleep increased by 7.5% after zolpidem and decreased by 4.4% after exercise. REM sleep decreased by 4.3% after zolpidem and increased by 2.4% after exercise.

Moderate effect sizes were observed for N2 sleep ($\eta^2 = 0.06$) and arousal index ($\eta^2 = 0.07$). N2 sleep decreased by 0.4% after zolpidem and increased by 4.2% after exercise. The arousal index decreased by 2.7 events/hour after zolpidem and increased by 1.3 events/hour after exercise. All other treatment comparison effect sizes for PSG data were small in magnitude.

Actigraphic estimation of sleep efficiency increased significantly after exercise treatment and actigraphic estimation of WASO decreased significantly after zolpidem treatment (►**Table 4**). However, no significant treatment-by-time effects were observed for any of these outcomes.

A moderate between-treatment effect size was found for actigraphic sleep latency ($\eta^2 = 0.13$). Compared with baseline, sleep latency decreased after exercise (5.4 minutes), but increased after zolpidem (2.9 minutes). All other effect sizes for actigraphic data were small in magnitude.

No significant differences between treatments were observed in the level of morning cortisol ($p > 0.05$).

Discussion

The present study compared the acute effects of moderate aerobic exercise *versus* zolpidem in patients with chronic insomnia. Non-inferiority of exercise versus zolpidem was observed for the PSG estimate of sleep latency. For all other comparisons, 95% CI was too wide to conclude the non-inferiority of exercise versus zolpidem. ANOVAs and effect

Table 2 Comparisons of before and after Zolpidem or exercise treatments, Sleep Diary, and Cortisol level

Outcome	Treatment	Baseline Mean ± S.D.	Post-treatment Mean ± S.D.	Difference Estimate	Difference 95% C.I.	Interaction Estimate	Interaction 95% C.I.	η^2
TST (h)	Zolpidem	5.50 ± 1.50	6.81 ± 1.67	**1.31**	[0.03; 2.59]	0.00	[-1.75; 1.76]	0.00
	Exercise	4.56 ± 1.27	5.88 ± 1.46	**1.31**	[0.11; 2.51]			
TIB (h)	Zolpidem	8.39 ± 0.83	8.50 ± 0.63	-0.14	[-070;0.42]	-0.38		
	Exercise	7.64 ± 0.93	7.77 ± 0.63	0.24	[-0.39;0.87]			
WASO (min)	Zolpidem	132.86 ± 96.21	50.86 ± 85.85	**-82.00**	[-153.16; -10.84]	32.00	[-65.44; 129.44]	0.04
	Exercise	127.50 ± 93.31	77.50 ± 85.19	-50.00	[-116.56; 16.56]			
SE (%)	Zolpidem	64.10 ± 19.26	80.76 ± 22.00	**16.66**	[3.69; 29.62]	-1.44	[-19.20; 16.31]	0.00
	Exercise	60.98 ± 17.45	76.20 ± 19.96	**15.21**	[3.08; 27.34]			
Sleep latency (min)	Zolpidem	47.14 ± 35.92	21.71 ± 18.27	**-25.43**	[-43.51; -7.35]	14.18	[-10.58; 38.94]	0.11
	Exercise	33.75 ± 15.98	22.50 ± 13.09	-11.25	[-28.16; 5.66]			
Cortisol level (mcg/dl)	Zolpidem	13.56 ± 4.13	11.99 ± 4.15	-1.57	[-4.59; 1.45]	1.41	[-2.75; 5.56]	0.03
	Exercise	12.11 ± 3.57	11.95 ± 5.04	-0.16	[-3.01; 2.69]			

Abbreviations: SE, sleep efficiency; TST, Total Sleep Time; WASO, wake after sleep onset.
Notes: A repeated-measures analysis of variance (ANOVA) was used for each outcome; **Bold** if significant at the α level of 0.05; $N = 15$ ($N = 8$ for Zolpidem group and $N = 7$ for Exercise group.

Table 3 Comparisons of before and after Zolpidem or exercise treatments, polysomnography data

Outcome	Treatment	Baseline Mean ± S.D.	Post-treatment Mean ± S.D.	Difference Estimate	Difference 95% C.I.	Interaction Estimate	Interaction 95% C.I.	η²
TST (min)	Zolpidem	415.00±38.89	452.50±37.47	37.50	[-6.80; 81.80]	13.44	[-47.45; 74.34]	0.01
	Exercise	353.89±59.45	404.83±34.09	**50.94**	[16.59; 85.30]			
WASO (min)	Zolpidem	61.00±28.44	31.88±14.74	**-29.12**	[-56.20; -2.05]	4.74	[-32.48; 41.95]	0.00
	Exercise	71.17±51.13	46.78±34.48	-24.39	[-49.92; 1.14]			
SE (%)	Zolpidem	85.65±6.10	91.79±3.66	**6.14**	[-0.14; 12.41]	0.47	[-8.15; 9.10]	0.00
	Exercise	82.17±11.94	88.78±7.28	**6.61**	[0.69; 12.53]			
Sleep latency (min)	Zolpidem	10.25±7.29	8.50±8.94	-1.75	[-5.00; 1.50]	-0.58	[-5.05; 3.89]	0.01
	Exercise	8.00±3.71	5.67±2.35	-2.33	[-5.40; 0.73]			
REM latency (min)	Zolpidem	110.88±62.11	171.75±100.15	**60.87**	[13.87; 107.88]	-58.43	[-123.04; 6.17]	0.20
	Exercise	131.00±46.91	133.44±56.99	2.44	[-41.87; 46.76]			
N1 sleep (%)	Zolpidem	6.84±7.24	3.96±2.05	-2.87	[-7.55; 1.80]	0.65	[-5.77; 7.07]	0.00
	Exercise	6.74±4.65	4.52±4.65	-2.22	[-6.63; 2.18]			
N2 sleep (%)	Zolpidem	47.21±11.42	46.83±11.14	-0.39	[-8.06; 7.29]	4.63	[-5.91; 15.18]	0.06
	Exercise	47.06±12.78	51.30±9.04	4.24	[-2.99; 11.48]			
N3 sleep (%)	Zolpidem	29.70±13.94	37.23±11.10	7.52	[-0.51; 15.56]	**-11.92**	[-22.97; -0.88]	0.26
	Exercise	32.68±15.26	28.28±10.39	-4.40	[-11.98; 3.18]			
REM sleep (%)	Zolpidem	16.29±5.73	11.99±4.86	-4.30	[-8.66; 0.06]	**6.68**	[0.69; 12.67]	0.27
	Exercise	13.54±5.04	15.92±4.09	2.38	[-1.73; 6.49]			
AHI (events/hour)	Zolpidem	4.90±3.41	5.30±4.27	0.40	[-1.64; 2.44]	0.02	[-2.78; 2.83]	0.00
	Exercise	3.08±2.03	3.50±2.77	0.42	[-1.50; 2.35]			
Arousal index (events/hour)	Zolpidem	17.74±8.19	15.08±4.80	-2.66	[-8.38; 3.06]	3.94	[-3.92; 11.80]	0.07
	Exercise	15.48±5.62	16.76±4.44	1.28	[-4.11; 6.67]			

Abbreviations: AHI, Apnea-Hypopnea Index; SE, sleep efficiency; TST, Total Sleep Time; WASO, wake after sleep onset.
Notes: A repeated-measures analysis of variance (ANOVA) was used for each outcome; **Bold** if significant at the α level of 0.05. $N = 15$ ($N = 8$ for Zolpidem group and $N = 7$ for Exercise group).

Table 4 Comparisons of before and after Zolpidem or exercise treatments, actigraphy data

Outcome	Treatment	Baseline Mean ± S.D.	Post-treatment Mean ± S.D.	Difference Estimate	Difference 95% C.I.	Interaction Estimate	Interaction 95% C.I.	η²
TST (min)	Zolpidem	410.38 ± 42.91	458.88 ± 33.24	48.50	[-7.16; 104.16]	-19.94	[-96.44; 56.55]	0.02
	Exercise	377.33 ± 74.36	405.89 ± 47.62	28.56	[-23.92; 81.03]			
Sleep latency (min)	Zolpidem	4.13 ± 2.47	7.00 ± 7.75	2.87	[-5.73; 11.48]	-8.32	[-20.14; 3.50]	0.13
	Exercise	10.89 ± 11.99	5.44 ± 3.84	-5.44	[-13.56; 2.67]			
SE (%)	Zolpidem	84.41 ± 5.45	91.47 ± 2.88	7.07	[-1.15; 15.28]	0.70	[-10.60; 12.00]	0.00
	Exercise	82.97 ± 10.22	90.74 ± 9.00	7.77	[0.02; 15.51]			
WASO (min)	Zolpidem	70.88 ± 29.07	34.38 ± 10.82	**-36.50**	[-68.16; -4.84]	10.06	[-33.46; 53.57]	0.02
	Exercise	56.78 ± 42.34	30.33 ± 40.42	-26.44	[-56.30; 3.41]			
Number of Awakening	Zolpidem	16.75 ± 5.42	12.13 ± 2.80	-4.63	[-10.32; 1.07]	1.29	[-6.54; 9.12]	0.01
	Exercise	13.22 ± 9.00	9.89 ± 6.92	-3.33	[-8.71; 2.04]			

Abbreviations: SE, sleep efficiency; TST, Total Sleep Time; WASO, wake after sleep onset.
Notes: A repeated-measures analysis of variance (ANOVA) was used for each outcome; **Bold** if significant at the α level of 0.05; $N = 15$ ($N = 8$ for Zolpidem group and $N = 7$ for Exercise group).

size comparisons showed little notable differences between treatments. Compared with acute exercise, the data showed no clear superiority for sleep improvement elicited by one of the most prescribed sleeping pills.

The results are consistent with previous studies in patients with chronic insomnia for both treatments. According to the literature, acute zolpidem treatment improves subjective and objective sleep.[33,34] In the present study zolpidem treatment improved objective WASO, SE, and REM latency, and subjective TST, WASO, SE, and sleep latency, showing significant improvement in the sleep of participants with chronic insomnia. Acute moderate-intensity aerobic exercise also elicits improvements in subjective[13] and objective sleep[13,14] in the same sleep variables. In the present study, acute exercise improved objective and subjective TST and SE.

Problems and risks related to zolpidem use and abuse have been reported in the literature over time. It includes an increase in mortality (mainly overdose, suicides, and quiet deaths at night), infections, accidents related to "sleep-driving," risk of falls, impairment in daytime performance, improved risk for depression, and cancer.[12] The author of this study also highlights that short-term use (one or two prescriptions) is associated with even greater risk per dose than long-term use.[12] In this way, acute exercise could be a better alternative to improve sleep in patients with insomnia, considering its similarity on sleep duration and sleep efficiency.

The increase in REM and a small increase in REM latency following exercise in the present study contrasts with the effects of acute exercise in good sleepers, for whom declines in REM and larger increases in REM latency are among the most consistent effects.[35] It is unclear why normal sleepers and individuals with insomnia would have disparate REM responses to acute exercise.

In the present study, a non-significant reduction in morning cortisol was observed after exercise and zolpidem. Previous studies have shown a reduction on a morning cortisol after 4-month of moderate-intensity aerobic exercise[23] and a significant correlation between the decrease in insomnia severity and the reduction in morning cortisol after 12 weeks of moderate-intensity aerobic exercise.[24] A previous study showed that diurnal cortisol of patients with chronic insomnia did not reduce after 12 months of zolpidem treatment.[36]

The main limitation of this study was the small sample size. The small sample size can limit the statistical power to observe significant treatment differences. However, the small effect size between groups showed similarity in the magnitude of effects of exercise and zolpidem on subjective sleep duration and sleep efficiency (evaluated by polysomnography and sleep diary). The small sample size could also result in the high CI, showing an inconclusive analysis of non-inferiority for many variables.

In conclusion, exercise was not significantly different from zolpidem for most sleep variables, suggesting that exercise impacts sleep in a similar way to zolpidem in patients with chronic insomnia. Considering the sleep health benefits of exercise, further research is warranted.

Conflict of Interest

The authors report no conflict of interest.

References

1 ICSD-3. American Academy of Sleep Medicine. International classification of sleep disorders. 2014;3th Edition

2 Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6(02):97–111

3 Riemann D, Spiegelhalder K, Feige B, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 2010;14(01):19–31

4 Vgontzas AN, Chrousos GP. Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. Endocrinol Metab Clin North Am 2002;31 (01):15–36

5 Javaheri S, Redline S. Insomnia and Risk of Cardiovascular Disease. Chest 2017;152(02):435–444

6 Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. Sleep 2009;32(04):491–497

7 Laugsand LE, Strand LB, Platou C, Vatten LJ, Janszky I. Insomnia and the risk of incident heart failure: a population study. Eur Heart J 2014;35(21):1382–1393

8 Hertenstein E, Feige B, Gmeiner T, et al. Insomnia as a predictor of mental disorders: A systematic review and meta-analysis. Sleep Med Rev 2019;43:96–105

9 Lovato N, Lack L. Insomnia and mortality: A meta-analysis. Sleep Med Rev 2019;43:71–83

10 Roux FJ, Kryger MH. Medication effects on sleep. Clin Chest Med 2010;31(02):397–405

11 Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4(05):487–504

12 Kripke DF. Hypnotic drug risks of mortality, infection, depression, and cancer: but lack of benefit. F1000 Res 2016;5:918

13 Passos GS, Poyares D, Santana MG, Garbuio SA, Tufik S, Mello MT. Effect of acute physical exercise on patients with chronic primary insomnia. J Clin Sleep Med 2010;6(03):270–275

14 Morita Y, Sasai-Sakuma T, Inoue Y. Effects of acute morning and evening exercise on subjective and objective sleep quality in older individuals with insomnia. Sleep Med 2017;34:200–208

15 Passos GS, Poyares D, Santana MG, et al. Effects of moderate aerobic exercise training on chronic primary insomnia. Sleep Med 2011;12(10):1018–1027

16 Reid KJ, Baron KG, Lu B, Naylor E, Wolfe L, Zee PC. Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. Sleep Med 2010;11(09):934–940

17 Youngstedt SD, Ito W, Passos GS, Santana MG, Youngstedt JM. Testing the sleep hygiene recommendation against nighttime exercise. Sleep Breath 2021;25(04):2189–2196

18 Chen LJ, Stevinson C, Fang SH, Taun CY, Ku PW. Effects of an Acute Bout of Light-Intensity Walking on Sleep in Older Women With Sleep Impairment: A Randomized Controlled Trial. J Clin Sleep Med 2019;15(04):581–586

19 Youngstedt SD, O'Connor PJ, Crabbe JB, Dishman RK. Acute exercise reduces caffeine-induced anxiogenesis. Med Sci Sports Exerc 1998;30(05):740–745

20 Meyer JD, Koltyn KF, Stegner AJ, Kim JS, Cook DB. Influence of Exercise Intensity for Improving Depressed Mood in Depression: A Dose-Response Study. Behav Ther 2016;47(04):527–537

21 Youngstedt SD, Dishman RK, Cureton KJ, Peacock LJ. Does body temperature mediate anxiolytic effects of acute exercise? J Appl Physiol 1993;74(02):825–831

22 Taylor RP, Olsen ME, Starnes JW. Improved postischemic function following acute exercise is not mediated by nitric oxide synthase in the rat heart. Am J Physiol Heart Circ Physiol 2007;292(01):H601–H607

23 Passos GS, Poyares D, Santana MG, et al. Exercise improves immune function, antidepressive response, and sleep quality in patients with chronic primary insomnia. BioMed Res Int 2014; 2014:498961

24 Ferreira WS, Santana MG, Youngstedt SD, et al. Effects of exercise training and exercise plus acupuncture on chronic insomnia: a feasibility study. Sleep Sci 2022;15(03):288–296

25 American Psychiatry Association. Diagnostic and statistical manual of mental disorders, 5 ed. Washington: DC:: American Psychiatry Association,; 2013

26 Morin CM, Vallières A, Guay B, et al. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. JAMA 2009;301(19):2005–2015

27 Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep 2012;35(02):287–302

28 Iber C, Ancoli-Israel S, Chesson AJ, Quan S. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester:: American Academy of Sleep Medicine; 2007

29 Jean-Louis G, Kripke DF, Mason WJ, Elliott JA, Youngstedt SD. Sleep estimation from wrist movement quantified by different actigraphic modalities. J Neurosci Methods 2001;105(02):185–191

30 McCall C, McCall WV. Comparison of actigraphy with polysomnography and sleep logs in depressed insomniacs. J Sleep Res 2012;21(01):122–127

31 Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ:: L Erbaum Associates,; 1988

32 Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DGCONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA 2012;308 (24):2594–2604

33 Kryger MH, Steljes D, Pouliot Z, Neufeld H, Odynski T. Subjective versus objective evaluation of hypnotic efficacy: experience with zolpidem. Sleep 1991;14(05):399–407

34 Huedo-Medina TB, Kirsch I, Middlemass J, Klonizakis M, Siriwardena AN. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. BMJ 2012;345:e8343

35 Youngstedt SD, O'Connor PJ, Dishman RK. The effects of acute exercise on sleep: a quantitative synthesis. Sleep 1997;20(03): 203–214

36 Roehrs T, Roth T. Hyperarousal in insomnia: pre-sleep and diurnal cortisol levels in response to chronic zolpidem treatment. Sleep Med 2019;61:52–56