Ecological validity of biomarkers in drug research

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CHAPTER 3

THE INTERACTIVE WALKWAY PROVIDES FIT-FOR-PURPOSE FALL RISK BIOMARKERS IN THE ELDERLY: COMPARISON OF ZOLPIDEM AND SUVOREXANT

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ABSTRACT

Dynamic balance assessments such as walking adaptability may yield a more realistic prediction of drug-induced falls compared to postural stability measurements, as falls often result from limited gait adjustments when walking. The Interactive Walkway (IWW) measures walking adaptability but sensitivity to medication effects is unknown. If proven sensitive and specific, IWW could serve as a biomarker for targeted fall-risk assessments in early clinical drug development.

In this 3-way crossover study, 18 healthy elderly (age: 65-80 years) subjects received 5 mg zolpidem, 10 mg suvorexant or placebo in the morning. Assessments were performed pre-dose and approximately hourly until 9 h post-dose. IWW assessments included an 8-meter walking test, goal-directed stepping, obstacle-avoidance, and tandem-walking. Other pharmacodynamic measurements were the Timed-Up-and-Go (TUG) test at a comfortable and fast pace, adaptive tracking, and body sway.

A decline in performance was observed for zolpidem compared to placebo for 3 h post-dose in IWW walking adaptability outcome measures, TUG, adaptive tracking, and body sway. For the IWW tasks, a decrease in walking speed (among others) was observed. IWW parameters were not affected by suvorexant compared to placebo at any time point. However, an increase of 9.8% (95%CI: 1.8%,18.5%) in body sway was observed for suvorexant compared to placebo up to 3 h post-dose.

The IWW successfully quantified drug effects of two hypnotic drugs and distinguished between zolpidem and suvorexant regarding their effects on walking. As a biomarker, the IWW demonstrated sensitivity in assessing dynamic balance and potential fall risk in early phase clinical drug development.

INTRODUCTION

Sleep disturbances can have serious adverse consequences in older adults. Increased risk of falls is among the most prevailing.[1] Approximately 28-35% of people aged 65 years and over fall annually, increasing to 32-42% for those over 70 years of age.[2] This risk of falling is increased with medications commonly prescribed for insomnia that are known to affect psychomotor functioning. Sleep medications such as benzodiazepines have been demonstrated to affect standing balance, increasing the risk of falls in the elderly.[3-6] (benzodiazepines OR, 1.57 (95%CI: 1.43; 1.72).[7] Benzodiazepines are positive allosteric modulators of the gamma-aminobutyric acid-A (GABA-A) receptors involved in the basal ganglia-thalamocortical systems and affect fine-tuning of motor commands.[8] In an elderly population, the consequences of a fall due to a loss of balance caused by drugs can be severe.

During early clinical drug development, postural stability is typically measured through anterior-posterior body sway during a quiet, upright stance. We have previously used the body sway test to demonstrate the effects of sleep deprivation,[9] alcohol,[10] benzodiazepines,[11,12] and other psychoactive agents[13] on body stability. Even though this body sway is a biomarker sensitive to drug effects, its relationship with common causes of falling is unclear.

Falls during walking and transfers predominantly result from inadequate interactions with the environmental context, leading to balance loss due to a trip, slip, or a misplaced step.[14-15] Walking adaptability thus seems to be an essential determinant of fall risk. Assessing fall-risk biomarkers incorporating such walking-adaptability interactions may, therefore, result in a stronger predictor of falls compared to body sway during quiet stance or other clinical tests such as the Timed-Up-and-Go (TUG) test. The Interactive Walkway (IWW) is an instrument developed to assess walking adaptability and walking-related fall risk by augmenting a multi-Kinect-v2 walkway with projected visual context (stepping targets, suddenly appearing obstacles) and parameterizing various fall-risk biomarkers, such as obstacle-avoidance margins and success rates based on markerless full-body 3D motion tracking.[16,17] IWW fall-risk assessment protocols comprise complementary environmental-context tasks such as avoiding suddenly appearing obstacles, precision stepping and tandem-walking tasks.

IWW outcome measures are sensitive for discriminating between freezing and non-freezing people with Parkinson's disease and healthy controls, as well as between people with stroke and healthy controls,

with differences in expected directions.[18,19] More relevant to the current study is the observation that IWW assessments improved the identification of prospective fallers compared to generic fall-risk factors and standard clinical test scores such as TUG, with poor obstacle-avoidance success rates and insufficient slowing down in tasks that demand precise foot placement as key predictors.[20] However, it is unknown whether such IWW fall-risk biomarkers are sensitive to sleep-medication effects. If so, the IWW could qualify as a valuable instrument for a targeted fall-risk assessment in early clinical drug development.

Orexin receptor antagonists are a new class of hypnotics, of which suvorexant and lemborexant are the first representatives registered for the treatment of insomnia in the United States, while daridorexant is the first available to patients in both US and Europe.[21] Suvorexant, lemborexant, and daridorexant are dual orexin receptor antagonists (DORAs) and inhibit orexin receptors alleviating the potential hyperarousal effect of orexin -A and orexin-B neuropeptides.[22–24] Benzodiazepines have a broader effect on the central nervous system (CNS) compared to DORAs with a specific target at the orexin system, reducing wakefulness. Based on differences in the mechanism of action, differences in fall-risk and balance can be expected.

This placebo-controlled study aimed at evaluating the use of the IWW as a biomarker for fall-risk studying the effect of 10 mg suvorexant and 5 mg zolpidem in 18 healthy elderly subjects. We expect that both drugs increase fall-risk biomarkers, especially in the first hours after intake, but less so for suvorexant, given that it is expected to have a smaller influence on psychomotor functioning than zolpidem.

METHODS

The study was registered at ToetsingOnline under NL76600.056.21 and approved by Foundation Beoordeling Ethiek Biomedisch Onderzoek, Assen, The Netherlands. All subjects gave written informed consent before the study started. The study was performed according to ICH-GCP guidelines, and the Declaration of Helsinki and its latest amendments. The study was conducted from 26 April 2021 to 25 June 2021 at CHDR and the Leiden University Medical Center (LUMC) in Leiden, The Netherlands.

Design

This study was a single-center, randomized, double-blind, placebo-controlled, three-way crossover exploratory study in 18 healthy elderly subjects. The study consisted of a medical screening visit and three one-day treatment periods (Figure S1). Subjects received a single dose of suvorexant 10 mg, zolpidem 5 mg or placebo during the study periods. An in-between period of at least six days was chosen to ensure sufficient washout from the drug with the longest half-life (i.e., 12 h for suvorexant).

A complete medical screening was performed at CHDR to assess a subject's eligibility for this study. All subjects underwent screening 21 to 1 day before the first dosing, consisting of medical history, physical examination, Mini-Mental State Examination (MMSE), clinical laboratory tests (blood chemistry, hematology, serology, and urinalysis), supine vital signs, urine drug screen, breath alcohol test, and electrocardiogram. In addition, the subjects were familiarized with all study activities, including the IWW, body sway, and adaptive tracking, to minimize learning effects during study execution.

At treatment periods, subjects arrived in the morning and stayed at the LUMC until they were discharged in the evening, approximately 11 h after admission. At check-in, eligibility was re-checked based on a urine drug screen, breath alcohol test, concomitant medication, and adverse event (AE) review. Vital signs and AEs were repeatedly recorded throughout the study to assess safety. Blood samples measuring suvorexant and zolpidem plasma concentrations were collected before and at 1, 2, 3, 5, 7, 8, and 9 h after dosing. Assessments for the IWW, adaptive tracking, and body sway were performed at 2 and 1 h pre-dose and at 1, 2, 3, 5, 7, 8, and 9 h after dosing.

Subjects

Healthy elderly female and male subjects between 65 and 80 years were recruited via media advertisement or from the CHDR subject database. Subjects were only included if they had a regular sleeping pattern, scored 25 or higher on the MMSE, did not have a fall more than three times during the past year or had neurological diseases and/or orthopaedic problems that could interfere with normal gait function. Potential subjects performed all assessments during screening and were excluded if there was any doubt on their ability to complete the task during the study. Furthermore, it was not allowed to use concomitant medications with a pronounced effect on the CNS. Subjects were also asked not to consume alcohol, caffeine or xanthine-containing beverages or use any nicotine-containing products within 24 h before each study visit. Treatment administration was done around eleven o'clock in the morning.

Treatments

The recommended dose of suvorexant is 10 mg, according to the prescribing information.[22] It is approved by the FDA as a treatment for insomnia. Its median peak concentration (C_{max}) occurs at around 2 h post-dose in the fasted state which was also implemented in this study. The elimination half-life ($T_{½}$) is approximately 12 h.[22]

Zolpidem is often used as an active comparator in studies with sleep-inducing agents that measure coordination, residual effects, and/or postural stability.[25,26] Zolpidem is a hypnotic to treat insomnia, with 5 mg being the recommended starting dose for the elderly. Zolpidem is a ligand of high-affinity positive modulator sites of GABA-A receptors. It selectively binds to α1-subunits of this ion channel. Following oral administration, zolpidem is rapidly absorbed, with the time to attain C_{max} reached within 0.5-3 h. The $T_{½}$ is approximately 2.4 h.[27]

Suvorexant was provided as 10 mg tablets, and zolpidem was supplied as 5 mg tablets. Both study medications were over encapsulated in Swedish orange capsules to maintain blinding. Placebo consisted of identical, lactose-filled capsules. Subjects began fasting minimally 2 h before until 2 h after each study drug administration. Water was allowed ad libitum.

Randomisation and blinding

Study staff and subjects remained blinded until the database was locked. A statistician not involved in the clinical study conduct performed block-randomization using SAS (Cary, NC, USA) version 9.4. Subjects were randomly assigned to one of six treatment sequences in a balanced study design. Subject numbers were sequentially assigned to participants after medical screening by blinded study staff.

Pharmacodynamic Assessments

Interactive Walkway

Fall-risk biomarkers were derived from various walking (adapt)ability assessments with the IWW. The IWW comprises four spatially and temporally integrated Kinect-v2 sensors with optimized inter-sensor distances,[17,28] providing markerless 3D full-body kinematics of various body points (e.g., ankles, spine base, and spine shoulder). The IWW was equipped with a projector (EPSON EB-585W, ultra-short-throw 3LCD projector, Epson Europe B.V., Amsterdam, The Netherlands) to augment the entire 8-m walkway with gait-dependent visual context, such as obstacles or a narrow beam, for the walking-adaptability tasks. Using a spatial calibration grid, the sensors and projector coordinate systems were spatially aligned to a standard coordinate system.[16] IWW data was sampled at 30 Hz using custom-written software utilizing the Kinect-for-Windows Software Development Kit (SDK 2.0). IWW fall-risk biomarkers were validated for unconstrained walking and walking-adaptability assessments[16,17] and were better able to identify fallers prospectively than standard clinical test scores such as TUG.[20]

Subjects performed the following IWW tasks (see Figure 1), outcome measures for each task were averaged over the repetitions:

8-METER WALKING TASK (8MWT) This included walking at a self-selected walking speed. Outcome measures were walking speed (cm/s), step length (cm), step width (cm), cadence (steps/min), and step time (s). Two repetitions were performed.

OBSTACLE-AVOIDANCE TASK This included avoiding suddenly appearing obstacles. Outcome measures were obstacle-avoidance margins (cm), success rate (%), and (normalized) walking speed (%). Five repetitions were performed, more than the other tasks, to provide more data on the success rate for the obstacles.

GOAL-DIRECTED STEPPING (GDS) TASK This included precision stepping onto a sequence of shoe-size-matched stepping stones in an irregular pattern. Outcome measures were stepping accuracy (cm) and (normalized) walking speed (%). Two repetitions were performed.

TANDEM-WALKING TASK This included walking on a line. Outcome measures were success rate (defined as the percentage of steps on the line, %), (normalized) walking speed (%), and mediolateral sway (cm). Two repetitions were performed.

TUG This included rising from a standard armchair, walking to a line on the floor 3 m away, turning, returning, and sitting down again. The outcome measure was completion time (sec). Two repetitions were performed at a comfortable and two at a fast-walking speed.

Subjects always started with the 8MWT, which enabled the researcher(s) to adjust the settings of the walking-adaptability tasks to one's gait characteristics to obtain a similar level of difficulty for each subject and

measurement time. All IWW tasks were performed at a self-selected comfortable walking speed, except for the TUG, which was also performed at a fast-walking speed.

Adaptive tracking

The adaptive tracking test was performed as described initially by Borland and Nicholson[29] using customized equipment and software (based on TrackerUSB hard-/software (Hobbs, 2004, Hertfordshire, UK)). Adaptive tracking is a pursuit-tracking task susceptible to many psychoactive drugs.[10,11,30–32] During the test, a circle moves randomly on a screen, and the subject is instructed to keep a dot inside the moving circle by operating a joystick. When successful, the speed of the moving circle increases. Conversely, the velocity is reduced if the subject cannot maintain the dot inside the circle. The average speed of the moving circle as a percentage of the maximum speed of the circle over 3.5 min was used for analysis.

Body Sway

Body sway during quiet standing was used to assess postural stability as previously described.[10,12] Anterior-posterior body sway was measured with closed eyes using a body sway meter (Celesco) based on the Wright taximeter.[33] All body movements over 2 min were integrated and expressed as millimetres of sway and recorded. This relatively simple test shows deteriorations of postural stability with CNS-depressants[10] and some improvements with stimulants.[13]

Pharmacokinetic Assessments

Plasma samples were analyzed by an independent bioanalytical laboratory (Analytisch Biochemisch Laboratorium BV, Assen, The Netherlands). Concentrations of suvorexant and zolpidem were quantified using validated liquid chromatography with tandem mass spectrometry methods with a lower limit of quantification of 1.00 ng/mL and 0.50 ng/mL, respectively, and coefficient of variation between 2.1 and 8.3%, and 0.2% and 3.3% respectively. More detailed description of the analysis is available in the Supplementary information.

Analysis

Pharmacodynamics

Statistical analyses were performed using the SAS Version 9.4 (SAS Institute INC., Cary, NC, USA)

Each parameter was analyzed with a mixed-model analysis of covariance with treatment, time, period, sex, and treatment by time as fixed factors and subject, subject by treatment, and subject by time as random factors and the (average) baseline measurement as a covariate. Assessments of the first three h post-dose (recorded at 1, 2, and 3 h) were combined to increase the power of the analysis for the contrasts covering the T_{max} of both drugs. The sample size for this study is based on a precision estimate using previous collected data of effects on body sway by DORA compounds and benzodiazepines.

The Kenward-Roger approximation was used to estimate denominator degrees of freedom, and model parameters were estimated using the restricted maximum likelihood method.

The general treatment effect and specific contrasts were reported with the estimated difference and the 95% CI, the least square mean (LSM) estimates, and the p-value. Graphs of the LSM estimates over time by treatment were presented with 95% CI as error bars and change from baseline LSM estimates.

The following contrasts were calculated within the model: Suvorexant up to 3 h – Placebo up to 3 h; Suvorexant at 5 h – Placebo at 5 h; Suvorexant 7 to 9 h – Placebo 7 to 9 h; Zolpidem up to 3 h – Placebo up to 3 h; Zolpidem at 5 h – Placebo at 5 h; Zolpidem 7 to 9 h – Placebo 7 to 9 h; Suvorexant up to 3 h – Zolpidem up to 3 h; Suvorexant at 5 h – Zolpidem at 5 h, and Suvorexant 7 to 9 h – Zolpidem 7 to 9 h. The results were not corrected for multiple testing.

Body sway (anterior-posterior sway in mm/2 min) data was natural log-transformed before entering the Mixed Model Repeated Measures (MMRM). LSM, LSM difference, and 95% CI were transformed back to their original scale (i.e., to geometric mean and geometric mean ratio expressed in percentage change).

Pharmacokinetics

PK variable programming was conducted with R 3.6.1 for Windows (R Foundation for Statistical Computing/R Development Core Team, Vienna, Austria, 2019). PK parameters were calculated from concentration data in mass/volume units. Parameters were calculated using noncompartmental analysis, using actual elapsed time from dosing to estimate individual plasma PK parameters. These parameters were: C_{max}, T_{max}, $T_{½}$, and the area under the concentration-time curve from time zero to the last quantifiable concentration time point (AUC_{last}). All PK data were summarised by treatment group

using descriptive statistics. Values were expressed as the mean ± SD for all parameters except T_{max}, which was presented as the median (range).

RESULTS

Participants

18 (nine male and nine female) healthy subjects were enrolled in the study. The mean age (range) of all subjects was 71.9 (66-88) years, and their mean BMI (range) was 25.44 (21.5-29.6) kg/m^2. Seventeen subjects were white, and one subject was African-American. Eleven participants were excluded during the medical screening. Reasons for exclusion were: high blood pressure (n=6), abnormal ECG (n=3) or other reasons (n=2). No subjects were excluded based on the training of the assessments. All subjects completed the study; therefore, the safety, PK-, and PD-analysis set consisted of 18 subjects (Table S1).

Pharmacodynamics

All analyses were performed on the change from baseline, with baseline defined as an average of the first two assessments on that day. The results of the body sway, adaptive tracking, TUG, and IWW tasks up to 3 h compared to placebo post-dose are presented in Table 1. The table includes the variables with at least one significant contrast for IWW. The table, including all results of the body sway, adaptive tracking, TUG, and IWW tasks compared to baseline, is presented in the Supplement (Table S2). None of the tasks included in this study showed any statistically significant results for the contrasts at 5 h post-dose and 7-9 h post-dose; these time points are therefore not presented here.

In general, the average walking speed by treatment was fastest in the 8MWT (115.8 – 121.4 cm/s) and slowest in the tandem-walking task (94.2 – 103.6 cm/s). For all IWW tasks, walking speed decreased significantly for zolpidem compared to both placebo and suvorexant. Between these two contrasts, the effect was stronger for zolpidem compared to placebo. The greatest and smallest differences in walking speed for zolpidem compared to placebo were found for the tandem-walking task (estimate of difference (ED): -9.41 cm/s (95% CI: -13.74; -5.07), Figure 2) and the obstacle-avoidance task (ED: -5.25 cm/s (-7.55; -2.96)), respectively. Speed differences for zolpidem compared to suvorexant were again greatest for the tandem-walking task (ED: -7.87 cm/s (-12.12; -3.61)) and smallest for the 8MWT (ED: -3.45 cm/s (-5.68; -1.23)). None of the IWW outcome measures differed significantly between suvorexant and placebo conditions. Shorter step lengths during the 8MWT were observed for zolpidem compared to both placebo (ED: -2.26 cm (-3.21; -1.30)) and suvorexant (ED: -1.85 cm (-2.80; -0.89)) conditions. Likewise, smaller leading-limb margins during the obstacle-avoidance task were observed for zolpidem compared to placebo (ED: -0.03 cm (-0.04; -0.01)) and suvorexant (ED: -0.02 cm (-0.03; -0.00)) conditions (see Figure 2). Finally, participants swayed more mediolaterally during the tandem-walking test with zolpidem than with suvorexant (ED: 0.54 cm (0.23; 0.84)), see Figure 2.

Compared to placebo (see Table S2), body sway during quiet standing was significantly increased for both zolpidem (ED: 122.3 mm, 35.2% (25.3%; 45.8%)) and suvorexant (ED: 34.1 mm, 9.8% (1.8%; 18.5%)) in the 3 h post-dose (Figure 2). Adaptive-tracking performance decreased significantly in the 3 h post-dose for zolpidem compared to placebo (ED: -3.60, (-4.52; -2.68)), but not significantly for suvorexant compared to placebo (ED: -0.77, (-1.70; 0.15). The TUG (both at comfortable (see Figure 2) and fast speed) increased significantly for zolpidem compared to placebo (ED: 0.68 sec, (0.38; 0.99) and ED: 0.43 sec (0.26; 0.60), respectively). The TUG did not increase for suvorexant compared to placebo but was significantly longer for zolpidem compared to placebo and suvorexant for both comfortable and fast speed (ED: 0.68 sec, (0.38; 0.99) and ED: 0.43 sec (0.26; 0.60), ED: 0.59 sec, (0.28; 0.90) and ED: 0.41 sec (0.24; 0.59), respectively).

Pharmacokinetics

For suvorexant and zolpidem, the mean concentration-time curve is depicted in supplementary figures. A summary of the PK parameters is provided in Table 2. The median T_{max} of zolpidem was 1h (Figure S2) and of suvorexant around 2 h (Figure S3). Individual concentrations showed accurate assessment of C_{max} in the first three hours for both drugs. The geometric mean C_{max} of zolpidem was 80 ng/mL (range 48 – 171 ng/mL) and of suvorexant 228 ng/mL (range 117 – 366 ng/mL). The AUC_{last} of zolpidem was 296 h*ng/mL (range 180 – 624 h*ng/mL) and the AUC_{last} of suvorexant was 1075 h*ng/mL (range 609 – 1896 h*ng/mL). The $T_{½}$ of zolpidem based on nine subjects was 2.3 h. The $T_{½}$ of suvorexant could not be calculated accurately as the estimation is only based on two subjects.

The concentration-effect curve of walking speed during the 8MWT (average per session) (Figure S4) and body sway (Figure S5) for zolpidem and suvorexant with a linear trendline shows a steeper relationship for zolpidem on both assessments. Other parameters were not analysed for this relation between concentration and effect.

Safety

Generally, both suvorexant and zolpidem were well tolerated. 19 AEs were reported for suvorexant, of which somnolence (n=12) was the most prevalent. 29 AEs were reported for zolpidem, of which somnolence (n=12), balance disorder (n=5), and dizziness (n=4) were the most prevalent. All AEs judged as related to the study medication were mild in intensity and self-limiting.

DISCUSSION

To evaluate the effect on walking adaptability of (newly) registered drugs, a sensitive biomarker with higher validity to real-life circumstances is preferred. Here, we present the results of a study in which two types of sleep-promoting drugs were evaluated versus placebo on three different levels of ecological validity using four biomarkers for postural stability and walking adaptability: the body sway, adaptive tracking, the TUG test, and the IWW. The PK, safety, body sway, and adaptive tracker data are all in accordance with the literature and the prescribing information of zolpidem and suvorexant. This underlines the reliability of the study. The walking speed of all IWW tasks and the performance parameters of the TUG, body sway, and adaptive tracking were all affected by zolpidem, indicating that zolpidem affected balance. In contrast, only body sway was affected by suvorexant, while IWW outcomes were not, indicating that this drug had a smaller effect on walking balance. After 3 h, no effects on stability and walking adaptability were detected for both sleep-inducing agents.

The IWW is a standardized test battery to measure fall-risk biomarkers, which was shown to differentiate between zolpidem and placebo with robust results. This biomarker, which not only considers postural stability during standing but also during walking, can therefore be used in early clinical drug development to detect effects on walking, postural stability, and possibly fall risk. The IWW might be preferred to static stability measurements, such as body sway, because of the high validity to daily activities. Additionally, the IWW can include different tasks, including stepping over obstacles or challenging participants to increase step length and width with stepping stones. This creates the opportunity to target specific drug effects relevant to drug development. Such options are limited or absent in the Step Quick Turn Test (SQTT, described below), TUG, or body sway task. On average, the walking speed under zolpidem was significantly decreased for all involved IWW tasks. The relation between walking speed and the GDS task was studied in a previous paper.[34] It can be argued that subjects prevented mistakes by reducing walking speed and that a translation to baseline walking speed is needed to accurately assess walking adaptability during this task. In addition to a significant change in walking speed, the significant change in the 8MWT step length indicates that participants took smaller steps, possibly to prevent the consequences of disbalance. The decrease in the margin of the leading limb during the obstacle-avoidance task indicates that participants stepped more closely to the obstacle. This could increase the risk of falling when stepping over real objects (and not 2D projections). The increased sway during the tandem-walking task indicates that more prominent movements of the upper body were made, which could be interpreted as more imbalance.

Although suvorexant numerically decreased the walking speed during the IWW tasks, the endpoints were not significantly altered compared to placebo. Similarly, the TUG task was significantly affected by zolpidem for up to 3 h post-dose but not by suvorexant (Table 1). Based on the data collected in this study, a sample size of 17 would suffice to differentiate between zolpidem and suvorexant (see statement in supplement). Because the IWW has not yet been fully validated, the current benchmark for clinical relevance is the well-known effect of zolpidem on increased fall-risk.[35] With the current study, a statistical difference between zolpidem and suvorexant has been shown with sufficient power, which indicates that suvorexant has a considerably lower impact on walking adaptability than zolpidem, which is clinically known to affect walking adaptability.

The psychomotor test battery for this study contained the adaptive tracking task and the body sway task. Both psychomotor tasks have been used before in clinical trials involving DORAs, and the results confirm previous findings.

In this study, for zolpidem and suvorexant compared to placebo, a significant increase in body sway was found for the first 3 h post-dose compared to placebo, while there was also a significant difference between zolpidem and suvorexant. Adaptive tracking showed a significant difference for zolpidem up to 3 h post-dose, the task did not show a significant difference for suvorexant.

The increase in body sway and decrease in adaptive tracking performance conform to previous findings in a study assessing morning dosing of daridorexant in healthy elderly subjects.[36] In that study, a single dose of 25 mg daridorexant showed an increased body sway in the first two hours

post-dose compared to the lower dose of 5 mg daridorexant or placebo. A similar result was found for almorexant 400 mg at 2 h post-dose; a return to baseline was seen after 6-8 h.[37]

In another previous study in healthy elderly, 10 mg zolpidem was compared with 8 mg ramelteon (melatonin receptor agonist) in a middle-of-the-night (MOTN) study using (among others) the SQTT.[38] This test is a shorter version of the TUG; it consists of two steps forward, a quick 180 degrees turn, and two steps back to the starting point. Only zolpidem caused a significant prolongation of the time to complete the SQTT and increased the sway during the task, which corresponds to the results found in this study.

In a MOTN-study, 10 mg zolpidem was compared to 5 mg and 10 mg Lemborexant.[39] A significant effect of zolpidem and lemborexant on body sway was detected in the MOTN and just after morning awakening. This supports the increase in body sway for zolpidem and suvorexant found in this study.

Comparing the results of the IWW in this trial with TUG and body sway, it may be concluded that the IWW does not have a greater sensitivity to detect the effects of zolpidem. However, the IWW is closer to fall-risk associated with activities of daily living, i.e., walking and transfers, and IWW therefore has more and direct clinical relevance for medication effects than body sway and other comparable lab-based assessments with more quantitative endpoints compared to the TUG. Because of the significant difference between suvorexant and placebo in the first 3 h post-dose, one may hypothesize that body sway is more sensitive than the IWW to the effects of suvorexant. The TUG showed similar results to the walking speed of the IWW tasks, and because of the lack of difference for other variables of the IWW tasks, the additional value of the IWW seems to be minor.

The difference in the effect of both drugs on the IWW and other assessments can be mainly explained by differences in the mechanism of action. Where suvorexant affects specifically the orexin system reducing wakefulness, zolpidem activates GABA-A receptors and neurotransmitters, which results in general sedation and muscle relaxation. This is also clearly visible in the concentration-effect graphs using the linear trendlines. Zolpidem shows a stronger impairing effect on both body sway and walking speed (see Figure S4 and S5).

Zolpidem and suvorexant were administered in the morning, which is different from the indication of sleep medication prescribed in the evening. Nevertheless, the PK parameters (Table 2) and safety reports were in line with the manufacturer's United States Prescribing Information (USPI) for zolpidem and suvorexant.[22,27]

Study limitations

Several limitations are to be considered when interpreting the results of this study. First, and perhaps most importantly, this study included freely and independently moving elderly participants, i.e., not young subjects or subjects with a real risk of falling. During the screening, participants answered questions regarding fall history, the use of walking aids, and any medical history events related to impaired walking or balance. Indicators of imbalance or a history of falling led to exclusion. The study population might not show characteristics of typical fallers (such as not adapting gait, not slowing down, or taking risks) when under the influence of medication. Even though this might not be the population naturally at risk, fall-risk biomarkers were sufficiently sensitive to show a structural effect of sleep-inducing agents in this relatively small sample size. In a population with a higher risk propensity, the effects of the drugs tested on walking ability could be expected to be larger rather than smaller.

Secondly, a previously proven relationship between walking speed and parameters indicated a higher risk of falling with higher walking speed.[34] Therefore, it might be argued that subjects prevented mistakes by reducing walking speed and that a translation to baseline walking speed is needed to accurately assess walking adaptability. Again, this nevertheless did not lead to absence of drug effects on walking ability so at higher walking speeds the drug effects would have been larger rather than smaller.

The effect of suvorexant might be different due to daytime dosing when the orexin system is more active, and additionally, hormone systems inducing sleep are naturally less active. However, fall-risk assessments in the previously mentioned MOTN studies show a similar relationship between benzodiazepine and DORA compounds.[39]

In conclusion, the effect of drugs affecting body stability were well detected using the IWW, both in terms of placebo-controlled differential effects of two types of sleep medication, as well as in terms of PD over time. This is the first study using the IWW to demonstrate the fit-for-purpose of the instrument to study the influence a single dose zolpidem and suvorexant on walking-adaptability related fall-risk parameters, showing it may be used as a new biomarker in clinical drug development to provide an early indication of drug-induced increased risk of fall.

REFERENCES

1 Hill EL, Cumming RG, Lewis R, Carrington S, Le Couteur DG. Sleep disturbances and falls in older people. Journals of Gerontology – Series A Biological Sciences and Medical Sciences. 2007;62(1): 62–6.

2 World Health Organization. WHO global report on falls prevention in older age [Internet]. 2007 [cited 2023 Jun 30]. Available from: https: //www.who.int/publications/i/item/9789241563536

3 Castleden CM, Allen JG, Altman J, St John-Smith P. European Journal of Clinical Pharmacology A Comparison of Oral Midazolam, Nitrazepam and Placebo in Young and Elderly Subjects. Eur J Clin Pharmacot. 1987;32: 253–7.

4 Nikaido AM, Ellinwood EH, Heatherly DG, Gupta SK. Age-related increase in CNS sensitivity to benzodiazepines as assessed by task difficulty. Psychopharmacology (Berl). 1990;100: 90–7.

5 Patat A, Brohier S, Zieleniuk I, Rosenzweig P, Perault MC, Vandel B, et al. Assessment of the interaction between a partial agonist and a full agonist of benzodiazepine receptors, based on psychomotor performance and memory, in healthy volunteers. Journal of Psychopharmacology. 1995;9(2): 91–101.

6 Swift C, Swift M, Ankier S, Pidgen A, Robinson J. Single dose pharmacokinetics and pharmacodynamics of oral loprazolam in the elderly. J clin Pharmac. 1985;20: 119–28.

7 Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the Impact of Nine Medication Classes on Falls in Elderly Persons. Essential Reviews in Geriatric Psychiatry. 2009;169(21): 1952–60.

8 Griffin CE, Kaye AM, Rivera Bueno F, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner Journal. 2013;13: 214–23.

9 Van Steveninck AL, Van Berckel BNM, Schoemaker RC, Breimer DD, Van Gerven JMA, Cohen AF. The sensitivity of pharmacodynamic tests for the central nervous system effects of drugs on the effects of sleep deprivation. Journal of Psychopharmacology. 1999;13(1): 10–7.

10 van Steveninck AL, Gieschke R, Schoemaker HC, Pieters MSM, Kroon JM, Breimer DD, et al. Pharmacodynamic interactions of diazepam and intravenous alcohol at pseudo steady state. Psychopharmacology (Berl). 1993;110(4): 471–8.

11 Van Steveninck AL, Schoemaker HC, Pieters MSM, Kroon R, Breimer DD, Cohen AF. A comparison of the sensitivities of adaptive tracking, eye movement analysis, and visual analog lines to the effects of incremental doses of temazepam in healthy volunteers. Clin Pharmacol Ther. 1991;50(2): 172–80.

12 Van Steveninck AL, Wallnöfer AE, Schoemaker RC, Pieters MSM, Danhof M, Van Gerven JMA, et al. A study of the effects of long-term use on individual sensitivity to temazepam and lorazepam in a clinical population. Br J Clin Pharmacol. 1997;44(3): 267–75.

13 Cohen AF, Burggraaf J, Van Gerven JMA, Moerland M, Groeneveld GJ. The use of biomarkers in human pharmacology (Phase I) studies. Vol. 55, Annual Review of Pharmacology and Toxicology. Annual Reviews Inc.; 2015. p. 55–74.

14 Niino N, Tsuzuku S, Ando F, Shimokata H. Frequencies and circumstances of falls in the national institute for longevity sciences, longitudinal study of aging (NILS-LSA). J Epidemiol. 2000;10: S90–4.

15 Talbot LA, Musiol RJ, Witham EK, Metter EJ. Falls in young, middle-aged and older community dwelling adults: Perceived cause, environmental factors and injury. BMC Public Health. 2005 Aug 18;5(86).

16 Geerse DJ, Coolen BH, Roerdink M. Kinematic validation of a multi-Kinect v2 instrumented 10-meter walkway for quantitative gait assessments. PLoS One. 2015;10(10): 1–15.

17 Geerse DJ, Coolen BH, Roerdink M. Walking-adaptability assessments with the Interactive Walkway: Between-systems agreement and sensitivity to task and subject variations. Gait Posture. 2017;54: 194–201.

18 Geerse DJ, Roerdink M, Marinus J, van Hilten JJ. Assessing walking adaptability in stroke patients. Disabil Rehabil. 2021;43(22): 3242–50.

19 Geerse DJ, Roerdink M, Marinus J, van Hilten JJ. Assessing Walking Adaptability in Parkinson's Disease: 'The Interactive Walkway.' Front Neurol. 2018 Dec 12;9.

20 Geerse DJ, Roerdink M, Marinus J, van Hilten JJ. Walking adaptability for targeted fall-risk assessments. Gait Posture. 2019 May 1;70: 203–10.

21 Hoyer D, Allen A, Jacobson LH. Hypnotics with novel modes of action. Br J Clin Pharmacol. 2020 Feb 1;86(2): 244–9.

22 FDA. USPI Suvorexant [Internet]. 2014. Available from: www.fda.gov/medwatch.

23 FDA. USPI Lemborexant [Internet]. 2019. Available from: www.fda.gov/medwatch.

24 FDA. USPI Daridorexant [Internet]. 2022. Available from: www.fda.gov/medwatch.

25 Drake CL, Durrence H, Cheng P, Roth T, Pillai V, Peterson EL, et al. Arousability and fall risk during forced awakenings from nocturnal sleep among healthy males following administration of zolpidem 10 mg and doxepin 6 mg: A randomized, placebo-controlled, four-way crossover trial. Sleep. 2017;40(7).

26 Greenblatt DJ, Roth T. Zolpidem for insomnia. Expert Opin Pharmacother. 2012 Apr;13(6): 879–93.

27 FDA. USPI Zolpidem [Internet]. 2007. Available from: http: //www.fda.gov/medwatch

28 Geerse D, Coolen B, Kolijn D, Roerdink M. Validation of foot placement locations from ankle data of a Kinect v2 sensor. Sensors (Switzerland). 2017;17(10): 6–9.

29 Borland R, Nicholson A. Comparison of the residual effects of two benzodiazepines (nitrazepam and flurazepam hydrochloride) and pentobarbitone sodium on human performance. Br J Clin Pharmacol. 1975;2(1): 9–17.

30 De Haas SL, De Visser SJ, Van Der Post JP, Schoemaker RC, Van Dyck K, Murphy MG, et al. Pharmacodynamic and pharmacokinetic effects of MK-0343, a GABAA α2,3 subtype selective agonist, compared to lorazepam and placebo in healthy male volunteers. Journal of Psychopharmacology. 2008 Jan;22(1): 24–32.

31 Gijsman HJ, Van Gerven JMA, Pieters MSM, Schoemaker HC, Kroon R, Tieleman MC, Ferrari MD, Spinhoven Ph, Van Kempen GMJ CAF. Pharmacokinetic and pharmacodynamic profile of oral and intravenous -meta-chlorophenylpiperazine in healthy volunteers. J Clin Psychopharmacol. 1998;18: 289–94.

32 Cohen A, Ashby L, Crowley D, Land G, Peck A, Miller A. Lamotrigine (BW430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam. Br J Clin Pharmacol. 1985;20(6): 619–29.

33 Wright BM. A simple mechanical ataxia-meter. J Physiol. 1971;218: 27P-28P.

34 Roerdink M, Geerse DJ, Peper C (Lieke) E. 'Haste makes waste': The tradeoff between walking speed and target-stepping accuracy. Gait Posture. 2021;85(January): 110–6.

35 Kolla BP, Lovely JK, Mansukhani MP, Morgenthaler TI. Zolpidem is independently associated with increased risk of inpatient falls. J Hosp Med. 2013;8(1): 1–6.

36 Muehlan C, Boehler M, Brooks S, Zuiker R, van Gerven J, Dingemanse J. Clinical pharmacology of the dual orexin receptor antagonist ACT-541468 in elderly subjects: Exploration of pharmacokinetics, pharmacodynamics and tolerability following single-dose morning and repeated-dose evening administration. Journal of Psychopharmacology. 2020 Mar 1;34(3): 326–35.

37 Hoever P, Hay J, Rad M, Cavallaro M, Van Gerven JM, Dingemanse J. Tolerability, pharmacokinetics, and pharmacodynamics of single-dose almorexant, an orexin receptor antagonist, in healthy elderly subjects. J Clin Psychopharmacol. 2013 Jun;33(3): 363–70.

38 Zammit G, Wang-Weigand S, Rosenthal M, Peng X. Effect of Ramelteon on middle-of-the-night balance in older adults with chronic insomnia. Journal of Clinical Sleep Medicine. 2009;5(1): 34–40.

39 Murphy P, Kumar D, Zammit G, Rosenberg R, Moline M. Safety of lemborexant versus placebo and zolpidem: Effects on auditory awakening threshold, postural stability, and cognitive performance in healthy older participants in the middle of the night and upon morning awakening. Journal of Clinical Sleep Medicine. 2020;16(5): 765–73.

FIGURE 1 Schematic overview of the Interactive Walkway tasks.

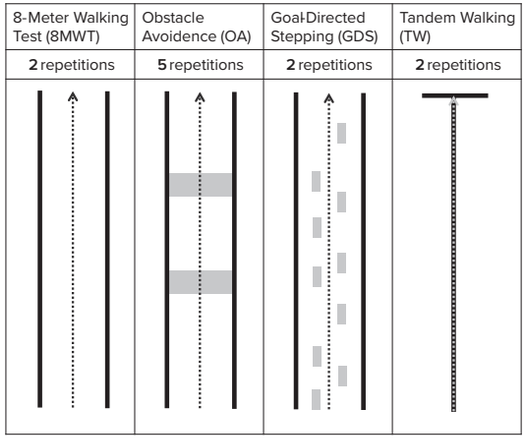

FIGURE 2 Graphical presentation of estimated means and 95% Confidence Intervals of results for placebo, zolpidem, and suvorexant. Top left: walking speed during tandem walking task. Top right: Margins leading limb during Obstacle Avoidance task. Bottom left: Time to complete the Timed Up and Go test. Bottom right: Total sway during the body sway task.

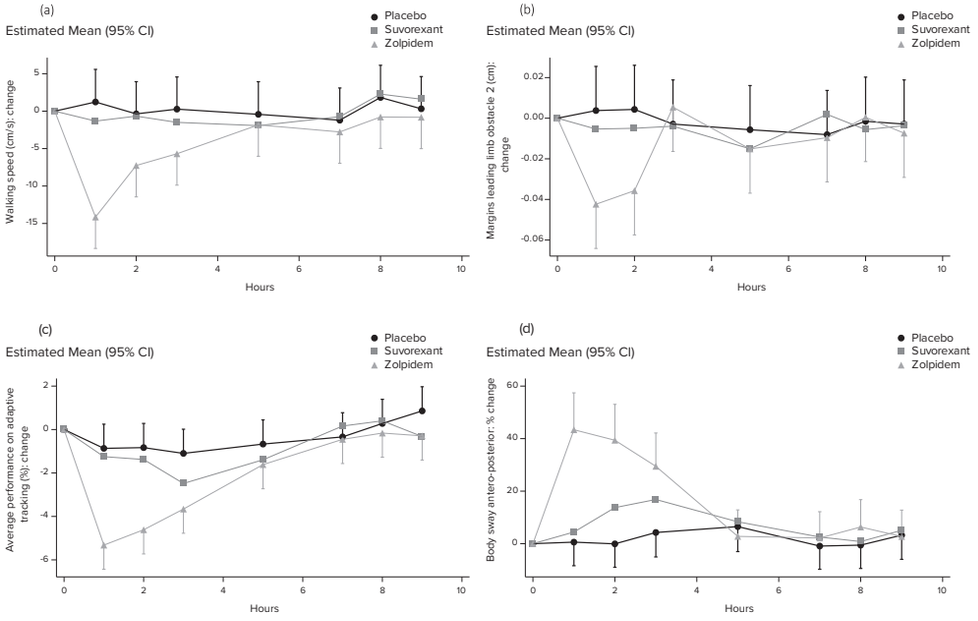

TABLE 1 Contrasts (95% CI) and p-value up to 3 h post-dose.

	zolpidem vs placebo	suvorexant vs placebo	zolpidem vs suvorexant	LSM placebo	LSM zolpidem	LSM suvorexant
Body sway (mm)	35.2% (25.3%,45.8%) p<.001	9.8% (1.8%,18.5%) p=.017	23.1% (14.1%,32.8%) p<.001	347.8	470.1	381.9
Adaptive tracking (%)	-3.60 (-4.52,-2.68) p<.001	-0.77 (-1.70,0.15) p=.101	-2.82 (-3.75,-1.91) p<.001	16.9	13.3	16.1
Interactive Walkway walking speed (cm/s)						
8-meter walking test	-5.56 (-7.77,-3.36) p<.001	-2.11 (-4.32,0.10) p=.061	-3.45 (-5.68,-1.23) p=.003	121.4	115.8	119.3
Goal-directed stepping	-8.12 (-11.14,-5.10) p<.001	-2.07 (-5.09,0.95) p=.173	-6.05 (-9.08,-3.02) p<.001	110.8	102.7	108.7
Obstacle-avoidance	-5.25 (-7.55,-2.96) p<.001	-1.43 (-3.71,0.86) p=.215	-3.83 (-6.12,-1.53) p=.002	115.1	109.8	113.7
Tandem-walking	-9.41 (-13.74, -5.07) p<.001	-1.54 (-5.87, 2.79) p=.475	-7.87 (-12.12,-3.61) p<.001	103.6	94.2	102.1
IWW 8MWT – Step Length (cm)	-2.26 (-3.21,-1.30) p<.001	-0.41 (-1.37,0.55) p=.392	-1.85 (-2.80,-0.89) p<.001	69.8	67.5	69.4
IWW OA – Margins Leading Limb (cm)	-0.03 (-0.04,-0.01) p<.001	-0.01 (-0.02,0.01) p=.381	-0.02 (-0.03,-0.00) p=.011	0.12	0.09	0.11
IWW TW – Sway (cm)	0.29 (-0.01,0.60) p=.062	-0.24 (-0.55,0.06) p=.116	0.54 (0.23,0.84) p<.001	3.13	3.42	2.89
Timed-Up and Go (sec)	0.68 (0.38,0.99) p<.001	0.09 (-0.22,0.40) p=.559	0.59 (0.28,0.90) p<.001	9.86	10.54	9.95
Timed-Up and Go fast (sec)	0.43 (0.26,0.60) p<.001	0.01 (-0.16,0.18) p=.895	0.41 (0.24,0.59) p<.001	7.25	7.68	7.26

IWW: Interactive Walkway; 8MWT: 8-meter walking test; OA: obstacle-avoidance; TW: Tandem-Walking

TABLE 2 Pharmacokinetic parameters of zolpidem and suvorexant.

	C_{max} (ng/mL) Mean(+/-SD)	T_{max} (h) Median(min-max)	$T_{½}$ (h) Mean(+/-SD)	AUC_{last} (h*ng/mL) Mean(+/-SD)
Zolpidem	82.8 (+/- 26.8) N=18	1 (1 – 3) N=18	2.9 (+/- 1.0) N=9	296 (+/- 104.5) N=18
Suvorexant	235.3 (+/- 61.1) N=18	2 (1 – 3) N=18	-	1074 (+/- 335.2) N=18

THE FOLLOWING SUPPLEMENTS ARE AVAILABLE ONLINE

Table S1 (Demographic characteristics), **Table S2** (All constrasts), **Figure S1** (Study design), **Figure S2** (Plasma concentration suvorexant), **Figure S3** (plasma concentration zolpidem), **Figure S4** (concentration-effect for walking speed), **Figure S5** (concentration-effect for body sway), and description of concentration analysis.

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