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Zolpidem improves task-specific dystonia: A randomized clinical trial integrating exploratory transcranial magnetic stimulation and [18F] FDG-PET imaging

Katarina Vogelnik Žakelj [a,b], Maja Trošt [a,c,d], Petra Tomše [c], Igor N. Petrović [e], Aleksandra Tomić Pešić [e], Saša Radovanović [e], Maja Kojović [a,d,*]

[a] Department of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia
[b] Institute of Clinical Neurophysiology, University Medical Centre Ljubljana, Ljubljana, Slovenia
[c] Department of Nuclear Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia
[d] Medical Faculty, University of Ljubljana, Slovenia
[e] Neurology Clinic, Clinical Center of Serbia, University of Belgrade, Belgrade, Serbia

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ABSTRACT

Background: Task-specific dystonia (TSFD) is a disabling movement disorder. Effective treatment options are currently limited. Zolpidem was reported to improve primary focal and generalized dystonia in a proportion of patients. The mechanisms underlying its therapeutic effects have not yet been investigated.
Methods: We conducted a randomized, double-blind, placebo-controlled, crossover trial of single-dose zolpidem in 24 patients with TSFD. Patients were clinically assessed using Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), Writers' Cramp Rating Scale (WCRS), and Visual Analogue Scale (VAS), before and after receiving placebo and zolpidem. Transcranial magnetic stimulation was conducted on placebo and zolpidem to compare corticospinal excitability – active and resting motor thresholds (AMT and RMT), resting and active input/output curves and intracortical excitability - cortical silent period (CSP), short-interval intracortical inhibition curve (SICI), long-interval intracortical inhibition (LICI) and intracortical facilitation (ICF). Eight patients underwent brain FDG-PET imaging on zolpidem and placebo.
Results: Zolpidem treatment improved TSFD. Zolpidem compared to placebo flattened rest and active input/output curves, reduced ICF and was associated with hypometabolism in the right cerebellum and hypermetabolism in the left inferior parietal lobule and left cingulum. Correlations were found between changes in dystonia severity on WCRS and changes in active input/output curve and in brain metabolism, respectively. Patients with lower RMT, and higher rest and active input/output curves exhibited better response to zolpidem compared to placebo.
Conclusions: Zolpidem improved TSFD by reducing corticomotor output and influencing crucial nodes in higher-order sensory and motor networks.

1. Introduction

Task-specific focal dystonia (TSFD) is a condition characterized by the loss of motor control specific to a particular motor skill [1]. Writer's cramp and musician's dystonia are its most common forms [2]. TSFD is a disabling disease that affects patients' quality of life and may even end their careers [3]. Current treatment options are limited and further research into new oral medications is warranted.

Zolpidem, a widely used hypnotic agent, enhances GABA transmission by selectively activating the GABA-A receptor α1 subunit [4]. One open-label study showed its effectiveness in primary focal and generalized dystonia, with most pronounced effect in hand dystonia [5]. The objective of this study was to further evaluate clinical efficacy of zolpidem in TSFD and to elucidate the mechanisms of its effects using transcranial magnetic stimulation (TMS) and brain FDG-PET. TMS allows in vivo assessment of drug effects on targeted neuronal circuits, while FDG-PET CT is neuroimaging technique that may capture the effects of treatment on regional brain metabolism [6–11].

* Corresponding author. Department of Neurology, University Medical Centre Ljubljana, Zaloška 2, 1000, Ljubljana, Slovenia.
E-mail address: maja.kojovic@kclj.si (M. Kojović).

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2. Methods

2.1. Standard protocol approvals, registrations, and patient consents

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia. Written informed consent was obtained from all participants according to the Declaration of Helsinki. The study was registered with ClinicalTrials.org (NCT04692285).

2.2. Study population

Consecutive patients with TSFD (writer's cramp and musician's dystonia) were recruited from adult movement disorders outpatient clinics. Patients treated with botulinum toxin injections within the last 3 months, those with other neurological diseases and those taking medications that could affect TMS measurements, were excluded. Any changes in medications other than study related drug intervention were not allowed.

2.3. Study design

This was a randomized, double-blind, placebo-controlled crossover two-centre study. Study visits took place at the University Medical Centre Ljubljana and the Clinical Centre of Serbia, from September 2017 to April 2021. Patients had two main study visits (on 5 mg zolpidem and placebo) for clinical examination and TMS, with a subset of patients also undergoing two additional visits (on 5 mg zolpidem and placebo) for FDG-PET brain imaging. Visits were spaced 7–10 days apart to allow for a washout period after zolpidem treatment. Sessions were scheduled at approximately the same time of day.

2.4. Clinical assessment

Patients with writer's cramp were assessed copying a standardized text. Patients with musician's dystonia were assessed playing the same music piece of their choice [12]. A blinded movement disorders expert rated dystonia from video recordings using Burke-Fahn-Marsden Dystonia Rating Scale – movement (BFMDRS-M; range 0–120) [13] in all patients and the Writing cramp rating scale – writing movement subscore (WCRS-M; range 0–28) [14] in writer's cramp cases. Video recordings were captured immediately before the administration of 5 mg zolpidem/placebo (clinical baseline) and 45 min after (clinical outcome), corresponding to the peak plasma concentration of zolpidem, which occurs between 45 and 60 min after ingestion [15].Subjective response was graded using a VAS from 0 % to 100 % (0 % no changes; 100 % normal, undisturbed writing/playing) [12,14]. Participants were also asked to evaluate their level of sleepiness using a VAS ranging from 0 to 10.

2.5. TMS measures of corticospinal excitability and intracortical excitability

TMS assessment lasted approximately 60 min and was performed post-treatment (immediately after clinical assessment) by a blinded investigator. Motor cortex contralateral to the affected hand in writer's and musician's cramp and contralateral to the dominant hand in embouchure dystonia, was stimulated. Single TMS pulses were applied using Magstim 2002 magnetic stimulator with monophasic waveform (Magstim Company, Carmarthenshire, Wales, UK). For double TMS pulses, two Magstim 2002 stimulators were connected with the Bistim module. A standard figure-eight coil was positioned tangentially to the skull and over the 'hotspot' point on the scalp, with the handle pointing backward at an angle of ~45° with respect to the sagittal plane. Hotspot point was defined as stimulation site where single TMS pulses produced largest motor evoked potentials (MEPs) recorded over the contralateral first dorsal interosseus (FDI) muscle. The hotspot was marked with skin marker on the participant's head and kept constant during experiment [16,17].The MEP amplitude in FDI muscle was measured with electromyography (EMG) with Ag–AgCl surface electrodes using a belly-tendon montage. The level of background EMG activity was monitored and trials with background EMG activity exceeding 50 μV were rejected online. The resting motor threshold (RMT) was determined as the minimum stimulator output intensity needed to evoke a MEP of at least 50 μV, observed in a minimum of 5 out of 10 consecutive trials [18].The active motor threshold (AMT) was established as the minimum stimulator output intensity necessary to elicit a MEP of at least 200 μV while maintaining a low-level contraction at 10 % of maximal voluntary contraction [18]. Motor hotspot, AMT and RMT were assessed during each visit. Input/output curves were assessed by recording 5 MEPs at each of 10 stimulation intensities, increasing in 10 % steps from 80 % to 170 % of RMT, delivered in randomized order [16]. Cortical silent period (CSP) curve was assessed during active input/output curve, while patients performed a constant contraction of FDI at 20 % of maximum voluntary contraction [19]. Short-interval intracortical inhibition curve (SICI curve), intra-cortical facilitation (ICF) [16] and long-interval intracortical inhibition (LICI) were assessed with the paired-pulse paradigm. For SICI paradigm, the intensity of the test stimulus (TS) was adjusted to 120 % of RMT while the intensity of the conditioning stimulus (CS) was 70 %, 80 %, 90 % and 100 % of AMT (delivered in randomized order), with an inter-stimulus interval (ISI) of 2 ms. ICF was assessed with the intensity of the TS adjusted to 120 % of RMT and the intensity of the CS to 80 % of AMT, with an ISI of 12 ms. LICI was assessed with the intensity of TS adjusted to 120 % of RMT while the intensity of the CS was 120 % of AMT, with an ISI of 150 m s. For SICI, ICF and LICI, 15 MEPs were collected in randomized order for CS-TS and for the TS alone. TMS data were analyzed by a blinded investigator.

2.6. FDG-PET imaging

Patients undergoing brain FDG-PET imaging were fasting overnight prior to scanning but were encouraged to drink plenty of water. FDG with activity 250 MBq was intravenously administered to the patients 60 min after receiving zolpidem/placebo. Patients were then placed to rest in a quiet dimly lit room with eyes closed for 30 min. Brain imaging was performed with low dose attenuation correction CT scan followed by 10 min resting state FDG-PET scan of relative glucose metabolism using Siemens Biograph mCT PET/CT scanner. Images were reconstructed using a Siemens TrueX-TOF iterative algorithm (6 iterations, 21 subsets) [20].

FDG-PET brain images were converted to Analyze format using MRIConvert (http://lcni.uoregon.edu/~jolinda/MRIConvert/) and preprocessed using SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/software/SPM12/), running in Matlab 7.0 (MathWorks Inc., Natick, MA). Spatial normalization using PET template in SPM12 was performed as well as smoothing using a Gaussian kernel of $10 \times 10 \times 10$ mm FWHM [20].

2.7. Outcome measures

Pre-specified study outcomes were: (i) clinical changes in dystonia severity; (ii) changes in corticospinal and intracortical excitability; and (iii) changes in brain metabolism. In addition, we examined the relationship between the before mentioned changes in cortical excitability, brain metabolism, and clinical measures of dystonia severity and tried to identify predictors for treatment response.

2.8. Randomization and blinding

For each investigation, patients were randomized into one of the two treatment sequences; zolpidem during first visit followed by placebo during second visit, or vice versa. For each patient, an inclusion number was provided to the investigators by an independent collaborator who

was also responsible for the unblinding process at the end of the study. Both, patients, and investigators were blinded for the treatment received. Zolpidem and placebo were supplied in capsules by Central Pharmacy of University Clinical Centre Ljubljana, they looked and tasted identical and were administrated orally. Video recordings, TMS and FDG-PET measures were analyzed in random order by blinded investigators.

2.9. Sample size calculation

G*power software and IBM SPSS Package 22 (IBM Corporation, New York, USA) were used for sample size calculation [21]. We used the data from the only previously published study on the clinical effects of zolpidem in task specific dystonia (as measured by changes in the BFMDRS) [5]. By assuming a size effect of 0.60 [5], one group, two within-subject measurements and a significance level set at $p \leq 0.05$, we calculated that the total sample size of 24 patients would suffice for power of 0.8.

2.10. Statistical analysis

IBM SPSS Statistics Version 22 and R version 4.3.2. were used.

2.10.1. Data preparation

For the analysis of TMS parameters the Boltzmann three-parameter sigmoidal function was fit to the input/output curves and CSP curve [19] and maximum MEP value (MEP max), peak slope (PS), and area under the fitted curve (AUC) were calculated [22]. Coefficients of determination (R^2) were calculated to assess the goodness of fit [23].

2.10.2. Main analyses

Separate Generalized Linear Mixed Models (GLMMs) with linear or gamma probability distributions were used to analyze the effects of intervention type (zolpidem versus placebo) on clinical scores (BFMDRS-M score and VAS for the entire group, and WCRS-M for writer's cramp) and TMS parameters. We controlled for treatment visit (1st visit vs. 2nd visit), visit-specific baseline clinical scores, age, and gender. Individual intercepts were included as random effects. Fixed coefficients (b) with confidence intervals (CI) are reported. For gamma distributions expotentiated (Exp) coefficients are reported. For clinical effects, p-values were corrected for multiple assessments using the Benjamini-Hochberg method. FDG-PET brain images on zolpidem were compared to corresponding placebo images using statistical parametric mapping (SPM12; paired *t*-test). Significant metabolic changes were identified if hypometabolic or hypermetabolic clusters contained more than 100 voxels and met a significance level of $p = 0.01$ (uncorrected) at both voxel and cluster levels. Results of TMS measures and FDG-PET brain images were not adjusted for multiple assessments, in line with exploratory study. Details are provided in Supplementary Appendix.

2.10.3. Sensitivity analyses

To assess the potential carry-over effect, we examined the Treatment x Visit interaction for all outcome measures. To examine placebo's impact on clinical scores, we conducted sensitivity analyses using separate GLMMs. The models included clinical scores as outcome variables, with placebo versus clinical baseline, gender, and age as fixed factors.

To address concerns about potential unblinding caused by sleepiness, we conducted a paired *t*-test comparing sleepiness levels between zolpidem and placebo. Additionally, we investigated whether self-reported sleepiness predicted perceived treatment allocation or influenced perceived improvement on the VAS scale.

2.10.4. Secondary analyses

To explore the mechanism of zolpidem effect on TSFD, within-participant correlations were performed between disease severity and TMS parameters or changes in relative regional glucose metabolism (which showed significant differences between zolpidem and placebo in the main analysis), using the Bland and Altman correction [24,25]. Multiple comparisons were addressed with Benjamini-Hochberg correction and adjusted *p* values are reported.

To identify predictors of patient response to zolpidem versus placebo, separate GLMMs were conducted. These models assessed the association between each predictor (including age, gender, and various TMS measures) and the change in dystonia severity, while controlling for baseline disease severity. As baseline TMS measures were not performed, we utilized TMS measures on placebo as an approximation. Significant predictors ($p < 0.05$) from the individual GLMM analyses were subsequently included in the final models for BFMDRS-M, WCRS-M, and VAS.

3. Results

3.1. Participants (Fig. 1)

24 TSFD patients were included (14 men), 17 with writer's cramp and seven with musician's dystonia (3 guitar players, 2 accordionists and 2 wind players). The mean age was 51.2 years (SD 16.9, range: 21–81). Detailed demographic and clinical data are provided in Supplementary Table 1. One female with writer's cramp and one male accordionist withdrew from the study after initial visit, both were assigned to the placebo first group.

In all GLMM analyses the effect of visit (1st vs. 2nd) was not statistically ($p > 0.05$), indicating that the order of treatment administration did not have a significant impact on the outcomes.

3.2. Clinical efficacy

Estimated marginal means of dystonia severity for zolpidem and placebo are shown in Fig. 2. Treatment effect (placebo versus zolpidem) emerged as a significant predictor across all clinical scores (Supplementary Table 1), indicating participants had significantly lower scores on BFMDRS-M (Exp (b) = 0.856, 95 % CI [0.765, 0.959], *p adj.* = 0.015) and WCRS-M (b = −2.283, 95 % CI [−4.370, −0.196], *p adj.* = 0.035), and greater improvement on the VAS scale (b = 12.725, 95 % CI [3.876, 21.574], *p adj.* = 0.015) on zolpidem compared to placebo.

3.3. TMS measures (Fig. 3)

3.3.1. Corticospinal excitability: motor thresholds, rest and active input/output curves

Treatment effect was not significant for RMT or AMT.

In all sessions in all subjects, the Boltzmann function provided a good fit (median $R^2 = 0.95$; IQR 0.89–0.97) [26]. On zolpidem, PS (Exp (b) = 0.318, 95 % CI [0.148, 0.679], $p = 0.005$) and AUC (Exp (b)0.715, 95 % CI [0.597, 0.860], $p = 0.001$) of the rest input/output curve, as well as MEP max (b = −1.285, 95 % CI [−2.205, −0.364], p = 0.009), PS (Exp (b) = 0.719, 95 % CI [0.573, 0.902], $p = 0.007$), and AUC (b = −35.368, 95 % CI [−65.208, −5.528], $p = 0.023$) of the active input/output curve were lower compared to placebo (Supplementary Table 3).

3.3.2. Intracortical inhibition: SICI curve, LICI and CSP

Treatment effect was not significant for any of the measures related to intracortical inhibition – SICI curve, LICI or CSP (Supplementary Table 4).

3.3.3. Intracortical facilitation: ICF

ICF was significantly lower on zolpidem compared to placebo (Exp (b) = 0.796, 95 % CI [0.666, 0.950], $p = 0.013$) (Supplementary Table 5).

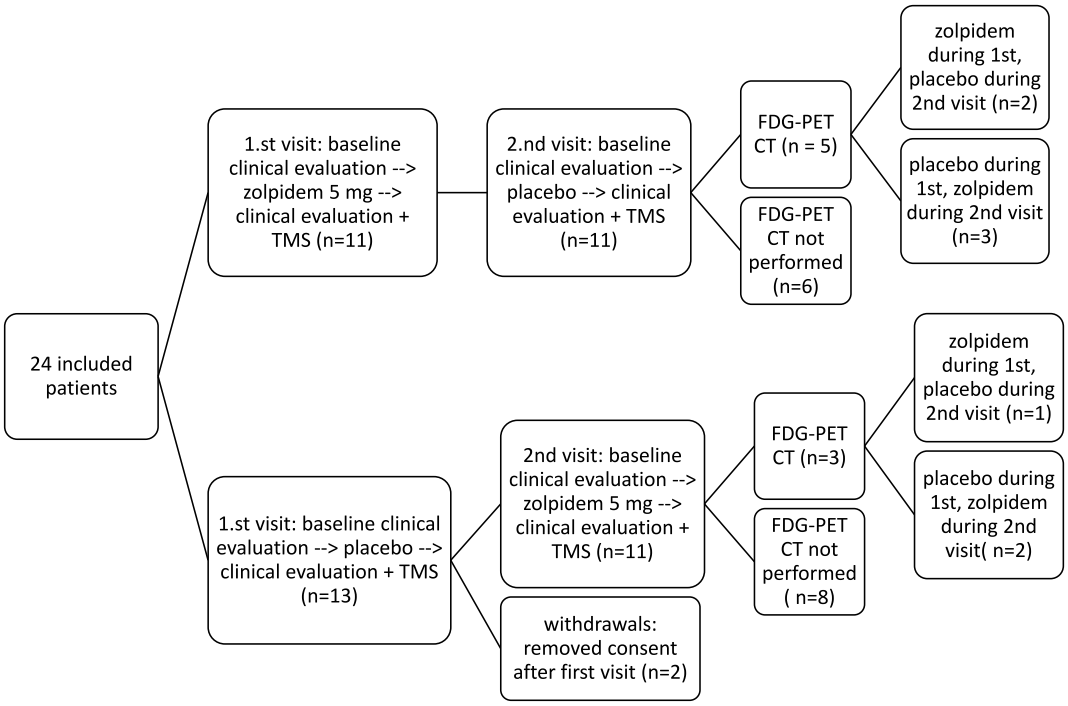

Fig. 1. Participant flowchart. TMS – transcranial magnetic stimulation; FDG-PET CT - 18F-fluorodeoxyglucose positron emission tomography/computerized tomography.

3.4. FDG-PET imaging (Fig. 4)

Eight patients underwent FDG-PET imaging. Compared to placebo, zolpidem induced distinct metabolic changes in three brain regions (p-voxel <0.01, p-cluster <0.01, uncorrected, cluster size >100). On zolpidem, hypermetabolism was found in the left inferior parietal lobule (BA40) (p-voxel = 6.09E-05, cluster size = 3201) and in the left dorsal anterior cingulate cortex (BA32) (p-voxel = 3.03E-05, cluster size = 1205), while hypometabolism was observed in the right posterior cerebellum (crus I/crus II) (p-voxel = 1.45E-05, cluster size = 1504) [27].

3.5. Sensitivity analyses

Sensitivity analyses revealed no evidence of carryover effects on either clinical or TMS measures. Additionally, BFDRS-M and WCRS-M scores did not show significant differences between the placebo and baseline conditions (Supplementary Table 6). Furthermore, no significant increase in sleepiness was observed with zolpidem compared to placebo (p = 0.07). Neither sleepiness nor its interaction with the administered drug significantly predicted perceived treatment allocation. Similarly, neither sleepiness nor its interaction with the administered drug significantly predicted VAS response (Supplementary Table 7).

3.6. Electrophysiological and metabolic correlates of zolpidem effect in TSFD (Supplementary Fig. 1)

In patients with writer's cramp, decrease of PS of the active input/output curve on zolpidem compared to placebo significantly correlated with decrease of disease severity on WCRS-M (r = 0.66, 95 % CI 0.25–0.87; p *adj.* = 0.012). In addition, reduced relative glucose metabolism in the right cerebellum (r = 0.72, 95 % CI 0.03–0.95; p *adj.* = 0.04), and increase in relative glucose metabolism in left inferior parietal lobule (r = -0.77, 95 % CI -0.96 to −0.14; p *adj.* = 0.04) and left cingulum (r = −0.83 95 % CI -0.97 to −0.30; p *adj.* = 0.03), all observed with zolpidem compared to placebo, correlated with reduced dystonia severity on WCRS-M score. No other significant correlations between WCRS-M score and TMS changes were found after adjusting for multiple comparisons (Supplementary Table 8).

No significant correlations between improvement on VAS or BFMDRS-M score and TMS measures were found (Supplementary Table 9).

No significant within-subject correlations were identified between metabolic brain changes and TMS measures. (Supplementary Table 8).

3.7. Predictors of zolpidem response (Supplementary Table 10)

For clinical improvement on BFMDRS-M, predictors included RMT, AMT, IO curve, and CSP were significant in separate analyses. However, when all predictors were included in the model simultaneously, lower RMT (Exp (b) = 0.973, 95 % CI [0.947, 0.999], p = 0.045) and higher IO curve (Exp (b) = 1.053, 95 % CI [1.026, 1.081], p = 0.001) remained significant and were associated with better treatment response. For improvement on WCRS-M score, only higher PS of active IO curve (b = −0.228, 95 % CI [−0.405, −0.052], p = 0.013) was found to be a significant predictor. No significant predictors were identified for improvement on VAS.

4. Discussion

4.1. Zolpidem effectiveness in TSFD

We showed that 5 mg single dose of zolpidem significantly improved TSFD. Improvement in writer's cramp was similar to the improvement reported in the literature with botulinum toxin injections [14]. Improvement in the whole group (writer's cramp and musician's dystonia), as assessed by BFMDRS-M and VAS, although significant, was smaller than reported in the literature [28,29]. This may be explained by a weaker response in musician's dystonia compared to writer's cramp [28] and/or insensitivity of BFMDRS-M to capture subtle changes during task performance.

4.2. Potential mechanisms of zolpidem effect in TSFD

The range of TMS parameters tested in the present study was based

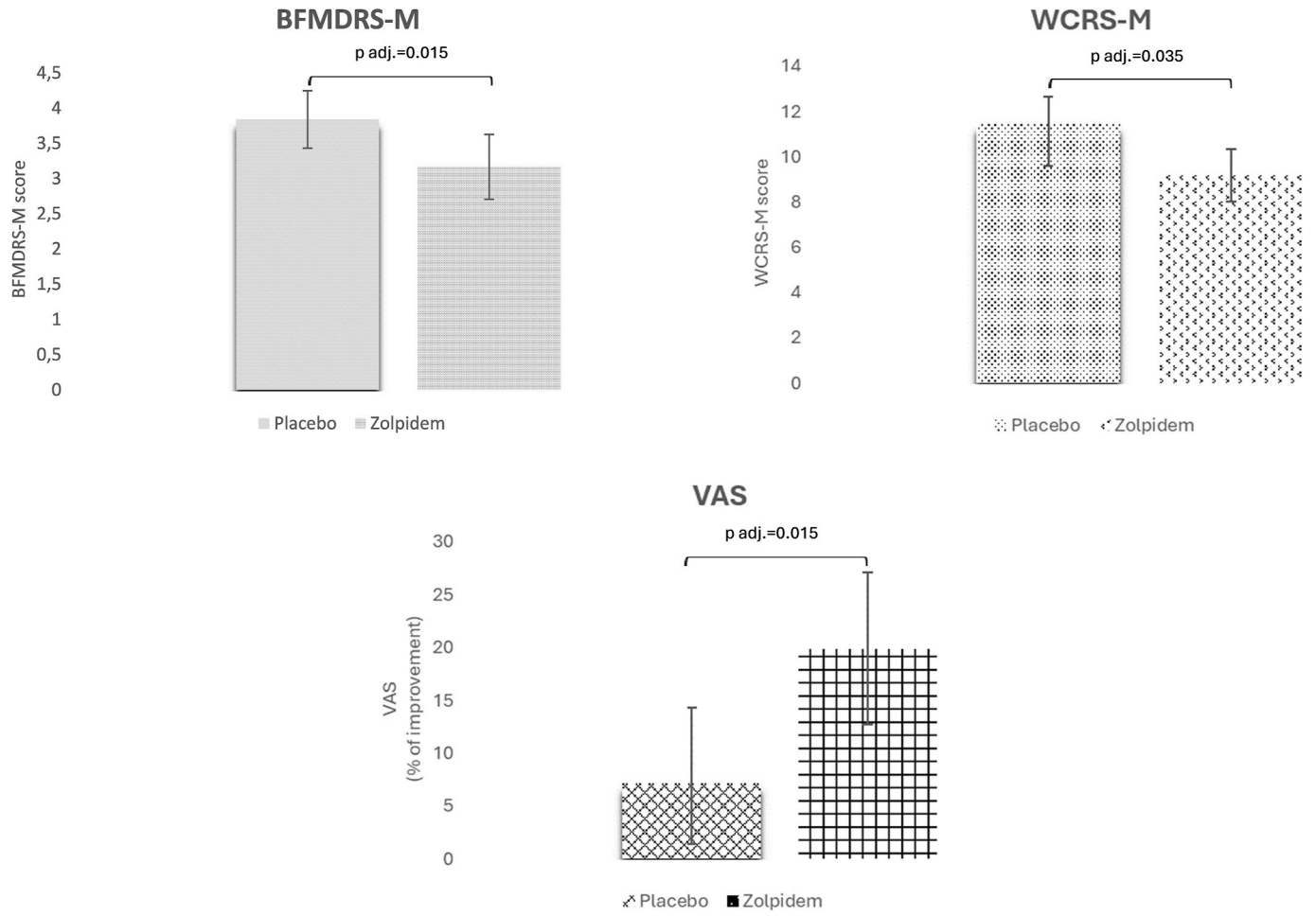

Fig. 2. Clinical effects. The impact of zolpidem and placebo on dystonia severity. Estimated marginal means with 95 % confidence intervals are represented. BFMDRS-M - Burke-Fahn-Marsden Dystonia Rating Scale – movement; WCRS-M - Writing cramp rating scale – writing movement sub-score; VAS: self-assessed improvement on visual analogue (VAS) scale from 0 to 100 %.

on previously reported abnormalities in TSFD [2].

We found that zolpidem effect was associated with changes in several TMS measures compared to placebo. Zolpidem decreased rest and active input/output curves, while it did not affect RMT or AMT. Zolpidem lowered ICF without affecting GABA-A or GABA-B intracortical inhibition measures (SICI, LICI or CSP). The reduction in the active input/output curve correlated with a decrease in dystonia severity on WCRS-M, implying that the observed effect was not a nonspecific outcome of zolpidem but rather linked to an improvement in dystonia.

The effect of zolpidem on input/output curves, in the absence of its effects on motor thresholds, is consistent with the established view that motor thresholds and input/output curves are governed by distinct mechanisms, shown to be differently modulated in previous pharmacological studies [30,31]. MEPs produced at motor threshold arise from monosynaptic connections between superficial excitatory pyramidal neurons and large pyramidal tract neurons [32]. Motor thresholds are influenced by agents blocking voltage-gated sodium channels. The lack of zolpidem's effect on motor threshold aligns with previous studies in healthy individuals and implies its lack of action on voltage-gated sodium channels [33–35]. On the other hand, MEPs produced at higher TMS intensities, as tested by input/output curve, arise through a more complex polysynaptic network of excitatory circuits controlled by inhibitory circuits, which may have been targeted by zolpidem [30]. The observed effect of zolpidem on reducing ICF without affecting SICI is both consistent with findings in healthy subjects [33–35] and with previous evidence indicating that pharmacological profile of ICF is similar to that of input/output curves, but different to that of SICI [30,36].

We attribute the absence of zolpidem effect on SICI to the existence of several GABA-A receptor subtype-specific circuits in the central nervous system. SICI is mediated via the a2-or a3-subtype of the GABA-A receptors, rather than the a1-subtype, on which zolpidem binds [37]. The absence of zolpidem effects on LICI and CSP also aligns with the pharmacodynamic properties of zolpidem, acting on the alpha-1 subunit of GABA-A receptors, while LICI and CSP depend on GABA-B intracortical inhibition [30,32]. TMS results of our study overall indicate that zolpidem may be effective in TSFD by decreasing the excitability of the primary motor cortex, which may result in the change of final output for the execution of motor programs, although causality cannot be stated due to lack of assessments.

FDG-PET imaging showed that zolpidem increased metabolism in the left anterior cingulate cortex and in the left inferior parietal lobule, while decreasing metabolism in the posterior lobe (Crus I/II) of the right cerebellum. These metabolic changes correlated with improvement of dystonia on WCRS- M scale. Cerebellum and anterior cingulate cortex are involved in motor processing [38,39], while inferior parietal lobule is part of sensory processing loop [38,40]. Previous metabolic [41,42] and fMRI [43,44] studies in writer's cramp have shown activation of these specific areas during finger movements and writing task. Loss of normal inhibitory interaction between inferior parietal lobule and motor cortex and changes in connectivity between crus I and crus II regions of motor cerebellum and cortical sensorimotor areas, have been

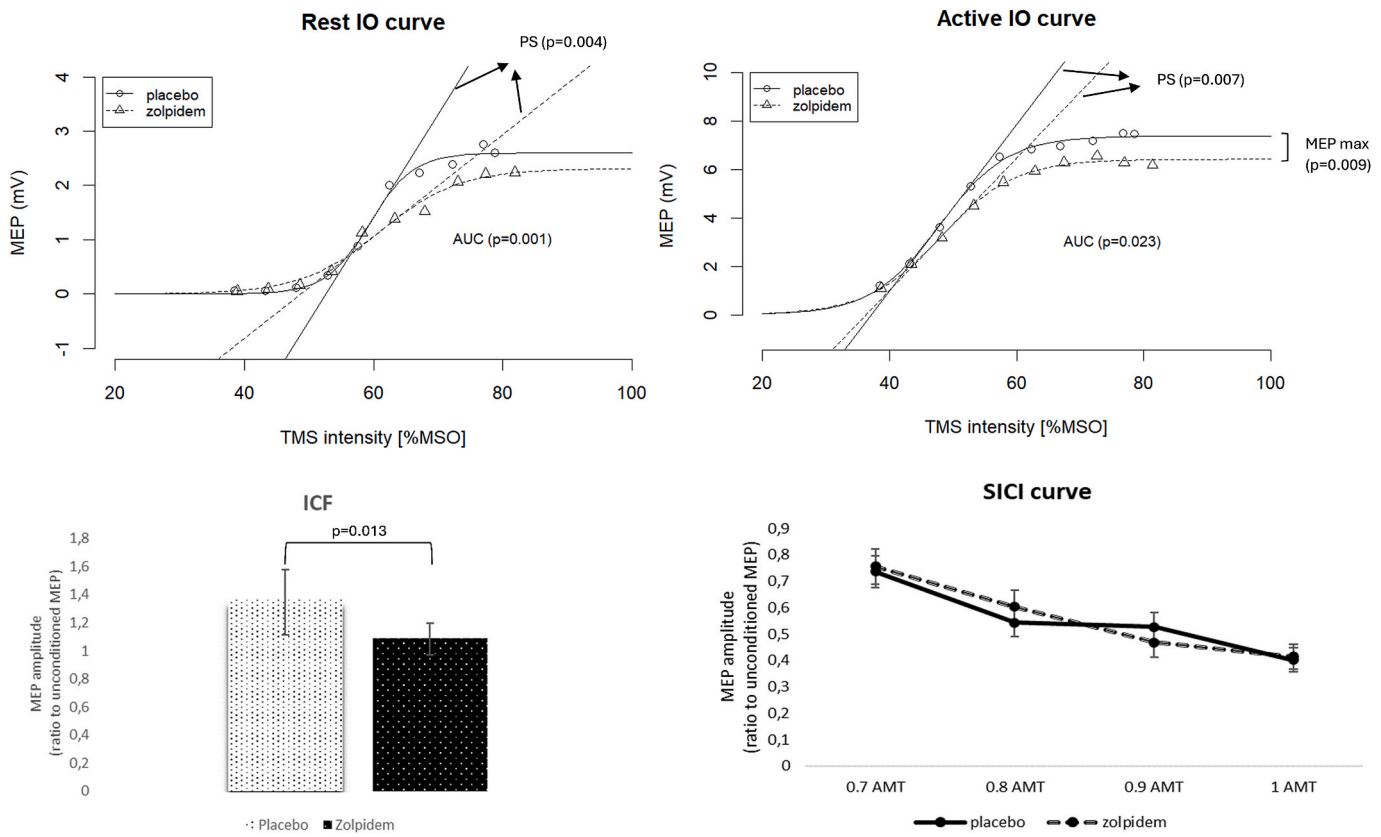

Fig. 3. Transcranial magnetic stimulation (TMS) measures. Zolpidem significantly decreased peak slope (PS) and area under the rest input/output curve (AUC) and maximal motor evoked potential (MEP max), peak slope (PS) and area under the active input/output curve (AUC). Zolpidem had no effect on short intracortical inhibition (SICI) curve but significantly reduced intracortical facilitation (ICF). IO – input/output; MSO – maximal stimulus output; AMT – active motor threshold; CS-conditioning stimulus.

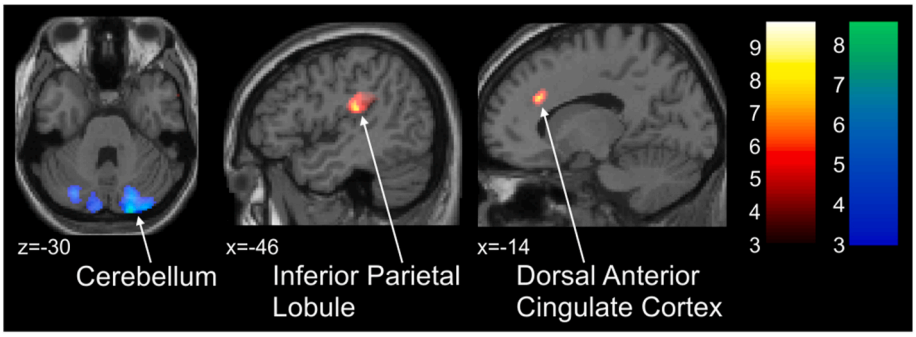

Fig. 4. Effects of zolpidem on brain metabolism measured by FDG-PET. Brain metabolism was different on zolpidem in comparison to placebo in three brain regions (p-voxel <0.01, p-cluster <0.01, uncorrected, cluster size >100). Relative metabolic increases are color-coded red to yellow (x = −16, y = 30, z = 28; and x = −44, y = −24, z = 18), whereas associated metabolic decreases are color-coded green to blue (x = 20, y = −90, z = −30). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

demonstrated with TMS connectivity [45] and functional MRI studies [46] in TSFD. Detected laterality of changes may be explained by the fact that seven out of eight patients had right-hand dystonia and aligns with prior research on focal hand dystonia, which found decreased GABA-A receptor density in specific brain regions contralateral to the symptomatic hand [47]. Moreover, metabolic imaging [38,42] and fMRI [43] changes in the left anterior cingulate cortex, left inferior parietal lobule and right cerebellum were all observed with dystonia improvement after botulinum toxin injections in TSFD, suggesting that the specific brain areas affected by zolpidem in our study are important in generation and expression of TSFD. Our FDG-PET findings thus indicate that zolpidem may exert its actions in TSFD via higher order sensory and motor circuits.

Currently, TSFD is viewed as an abnormality of higher-order sensory-motor integration [48], while classical neurophysiological markers of dystonia at the motor cortical level, such as increased gain of the input/output relationship and disrupted balance between intracortical inhibition and facilitation, may be downstream result of the higher-order deficits. It is tempting to suggest, that zolpidem exerts its effectiveness in TSFD, by its primary action on abnormally functioning higher-order sensory and motor circuits, which then leads to downstream changes within the primary motor cortex, modifying the final output for dystonic behavior. However, no relationship was found between metabolic brain changes and TMS parameters to substantiate this

hypothesis (although the lack of correlation may be due to smaller FDG-PET sample size) and improvement of TSFD on zolpidem may as well result from its independent effect on both lower- and higher-order dysfunctional motor skill network.

4.3. Electrophysiological predictors of zolpidem effectiveness in task specific dystonia

Patients with lower RMT, higher plateau of rest input/output curve and steeper active input/output curve, responded better to zolpidem. Thus, zolpidem's exerted the most favorable therapeutic response in individuals exhibiting heightened corticospinal excitability, indicating that this may be the primary abnormality targeted by zolpidem's pharmacodynamic properties.

4.4. Study limitations

Our study has several limitations. First, we included patients with writer's cramp and musician's dystonia (including musician's cramp and embouchure), introducing heterogeneity in the studied sample. This decision was influenced by the rarity of the disease and the recognized shared pathophysiological basis across various TSFD manifestations [49]. Thus, larger studies should confirm zolpidem effectiveness in musician's dystonia, which was underrepresented in our sample. Second. the sample was also heterogenous regarding participants' age, reflecting typical demographic profile of the disease, where symptoms usually emerge between the ages of 30 and 50, persisting throughout life [50]. To address potential variability in treatment response, age was included as a fixed factor in our analyses. Third, our study assessed the immediate effects of a single administration of zolpidem and the possible long-term benefit of zolpidem in TSFD remains to be determined in studies with longer follow-ups. Forth, TMS data collection was completed within 2 h after treatment administration. Although this time frame falls within zolpidem half-life window (2.8 h, ranging from 1.62 to 4.05 h) [51], individual metabolism rates may vary and our results may not entirely capture all potential effects of zolpidem. Fifth, zolpidem sedative effect could have unmasked blinding. To address this concern, we used a low 5 mg dose of zolpidem and in addition, controlled for the possible unblinding effect of sleepiness by recording subjective feeling of sleepiness on placebo and zolpidem. Although higher sleepiness was reported on zolpidem than on placebo, the difference was not significant. On the other hand, low 5 mg dose of zolpidem, used to balance the need for therapeutic effects with the risk of unblinding, was likely insufficient for optimal therapeutic response [52,53]. However, even with this dosage, we demonstrated zolpidem symptomatic effect in TSFD and the neurophysiological basis for detected improvement. Possibly, use of higher dosages might yield superior clinical effects and influence additional TMS and FDG-PET measures, providing more insight into mechanisms of zolpidem effect in TSFD. Sixth, objective assessment of any treatment efficacy in TSFD is challenging. Despite experiencing difficulties with specific task, patients can usually preform motor task satisfactorily by using tricks, i.e., by holding the pen differently. Many symptoms may relate to discomfort, which is difficult to visualize and rate. Due to these reasons and the absence of a standardized objective assessment tool for musician's dystonia, we also relied on the subjective assessment using VAS. However, it was previously demonstrated that in TSFD, subjective response is largely concordant with objective testing [14,28]. Seventh, our study primarily assessed clinical improvements, while exploring underlying mechanisms with TMS and FDG-PET. Our sample size calculation was based on the only available study assessing zolpidem clinical effects in heterogenous dystonia population. The limitation is the lack of sample size calculation for specific patient subsets and for TMS and FDG-PET imaging [54]. In particular, FDG-PET imaging subset might be underpowered for additional effects, although its size aligns with previous studies [9,10]. Larger multicenter studies are needed for deeper insights, but our findings provide valuable insights, given the challenges in recruiting larger cohorts in this rare condition. Eight, due to our study's design (lacking a control group), we couldn't ascertain differences in TMS measures between our patients and age-matched normal subjects. However, our primary interest was to investigate the change in TMS measures in response to zolpidem and in this context, we considered that a comparison group of healthy controls treated with zolpidem and placebo would not been ethically justified. Finally, although we accounted for baseline dystonia severity in the clinical assessment, we did not conduct baseline TMS measurements and baseline FDG-PET imaging. Such a study design was implemented with the aim of reducing the duration of experiments and thus mitigating confounding factor of sleepiness. Since in crossover trials, within subject variations are expected to be eliminated when comparing post-treatment outcomes of the same subjects from different periods, baseline measures generally have minimal impact on the efficiency of statistical analyses in crossover trials [55,56]. Additionally, including baseline in the FDG-PET study would have resulted in a one-time larger radiation exposure without a significant gain in information. Also, our sensitivity analysis showed that placebo had no effect on clinical measures, therefore the effects of placebo on TMS and FDG-PET measures are unlikely. We thus regard TMS and FDG-PET imaging assessments conducted under placebo as a valid approximation of the baseline condition.

5. Conclusions

A single dose of zolpidem (5 mg) significantly improved TSFD compared to placebo, suggesting that zolpidem might be efficient for TSFD patients in whom other treatment options didn't prove effective or in those who would prefer to take the medication on an as-needed basis (e.g. musicians before performance). Through the integration of TMS and metabolic brain imaging, our study provides first evidence that zolpidem exerts its clinical effect in TSFD by decreasing motor cortical excitability and by influencing major nodes in the higher-order sensory and motor network.

Data availability statement

Anonymized data on which this article is based will be shared on request with any appropriately qualified investigator.

Ethical standards

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia. Written informed consent was obtained from all participants according to the Declaration of Helsinki.

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CRediT authorship contribution statement

Katarina Vogelnik Žakelj: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Maja**

Trošt: Writing – review & editing, Writing – original draft, Conceptualization. **Petra Tomše:** Writing – review & editing, Writing – original draft, Formal analysis. **Igor N. Petrović:** Writing – review & editing, Resources. **Aleksandra Tomić Pešić:** Writing – review & editing, Resources. **Saša Radovanović:** Writing – review & editing, Resources. **Maja Kojović:** Writing – review & editing, Writing – original draft, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Appendix A. Supplementary data

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