Association between psychotropic medication and sleep microstructure: evidence from large population studies

Simon Hartmann, PhD[1, 2], Liborio Parrino, MD, PhD[3], Kristine Ensrud, MD, MPH[4, 5], Katie L Stone, PhD[6], Susan Redline MD, MPH[7], Scott Clark, FRANZCP, PhD[2], Mathias Baumert, PhD[1]

1. The University of Adelaide, School of Electrical and Electronic Engineering, Adelaide, Australia
2. The University of Adelaide, Discipline of Psychiatry, Adelaide Medical School, Adelaide, Australia
3. Sleep Disorders Center, Department of Neurology, University of Parma, Parma, Italy
4. Center for Chronic Disease Outcomes Research, Veterans Affairs Medical Center, Minneapolis, Minnesota, USA
5. Department of Medicine and Division of Epidemiology, University of Minnesota, Minneapolis, Minnesota, USA
6. California Pacific Medical Center Research Institute, San Francisco, CA, USA
7. Departments of Medicine and Neurology, Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Address for Correspondence:
Simon Hartmann,
Discipline of Psychiatry, Adelaide Medical School,
The University of Adelaide, Level 6, Adelaide Health and Medical Sciences Building,
Adelaide, SA 5005, Australia.
Email: simon.hartmann@adelaide.edu.au.

Address of Institution:
The University of Adelaide
Adelaide, SA 5005, Australia

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Abstract

Study Objectives: To assess the association between psychotropic medications and sleep microstructure in large community-based cohorts of older people.

Methods: We analyzed overnight polysomnograms of 381 women from the Study of Osteoporotic Fractures (SOF) and 2,657 men from the Osteoporotic Fractures in Men Sleep Study (MrOS), who either used no psychotropic medication (n=2,819), only benzodiazepines (n=112), or only selective serotonin reuptake inhibitors (SSRI) (n=107). Sleep microstructure (cyclic alternating pattern, CAP) was compared between the no medication group and psychotropic medication groups using the Mann-Whitney U-test. Significant differences were investigated using multivariable linear regression adjusted for confounders.

Results: CAP rate, arousal index, apnea-hypopnea index, and the frequency of slow, low-amplitude electroencephalography activation phases were significantly lower in MrOS participants using benzodiazepines than participants not taking psychotropic medication. SSRI users in MrOS experienced no altered sleep microstructure compared to those with no psychotropic use. SOF participants using benzodiazepines did not show similar associations with sleep microstructure. However, SSRI users from SOF had a significantly higher frequency of rapid, high-amplitude electroencephalography activation phases (A2+3) and periodic limb-movement index than participants not taking psychotropic medication. Multivariable linear regression adjusted for demographic, lifestyle, mood disorders, and health variables indicated additional significant associations between CAP rate and A2+3 index, respectively, and benzodiazepine usage in older men, and between CAP rate and SSRI usage in older women.

Conclusions: We identified significant associations between sleep microstructure and psychotropic drugs in MrOS and SOF highlighting the importance of comprehensive sleep analysis, including CAP. Our results may help to better understand the differences in sleep-wake mechanisms based on psychotropic usage.

Keywords: cyclic alternating pattern, benzodiazepines, selective serotonin reuptake inhibitors, sleep studies,

sleep-wake mechanisms

Brief summary

Current Knowledge/Study Rationale: Psychotropic drugs can significantly influence sleep, in particular sleep architecture. However, little is known about the association between psychotropic drugs and sleep microstructure across the older population. Here, we analyzed 3,038 recordings from two large community-based cohort studies to study the impact of psychotropic drugs on sleep macro- and microstructure in older individuals.

Study Impact: Multivariable linear regression adjusted for for demographic, lifestyle, and health variables revealed that the intake of benzodiazepines was associated with less fragmented sleep in older men. The intake of selective serotonin reuptake inhibitors was associated with a rise in rapid, high-amplitude EEG activation phases and periodic limb movements in older women. CAP analysis can amend the understanding of sleep-wake mechanism differences based on psychotropic medication with possible future indications for psychiatric disorder treatment.

Introduction

Sleep disorders such as insomnia are strongly associated with psychiatric disorders. The National Institute of Mental Health Epidemiologic Catchment Area study reported a prevalence of psychiatric disorders of 40.0% in participants with insomnia and 46.4% in participants with hypersomnia as compared to 16.4% of participants with no insomnia.[1] A study of people with insomnia by Ohayon *et al.* found that 28% reported being currently diagnosed with a mental health disorder, and 25.6% had a history of psychiatric illness.[2]

Psychotropic medications are commonly used to manage mental illness. Their interactions with various receptors in histaminergic and muscarinic cholinergic pathways,[3] the modulation of various monoamines,[3] and the binding of barbiturates, benzodiazepines, and neurosteroids on the $GABA_A$ receptor complex[4] can result in a significant impact on sleep physiology. As insomnia constitutes a core component of common disorders such as major depressive illness,[5] psychotropic treatment plans should consider healthy sleep as part of treatment plans. Studies investigating the effect of psychotropic drugs on sleep macrostructure commonly report associations with sleep macro-architecture, specifically sleep latency, wake after sleep onset (WASO) time, sleep efficiency, rapid eye movement (REM) latency, and REM density.[6] Previous studies have shown that benzodiazepines have sleep-promoting effects by reducing sleep onset latency, WASO time, and stage shifts[7] and are the most frequently prescribed drugs for insomnia.[8] Trazodone, a serotonin antagonist and reuptake inhibitor antidepressant has demonstrated a similar sleep-promoting effect resulting in an increase in sleep continuity with almost no effect on REM sleep.[6] It is often used “off-label” as a sleep aide despite a lack of evidence of its effectiveness.[9] On the contrary, the acute intake of selective serotonin reuptake inhibitor (SSRI) and monoamine oxidase inhibitor antidepressants increases REM onset latency, reduces the overall time spent in REM sleep, and increases the risk of restless legs syndrome, periodic limb movement, REM sleep behavior disorder, and REM sleep without atonia.[6,10,11] In contrast, tricyclic antidepressants (TCA) have shown a variable effect on sleep based on their sedating and alerting nature.[6,12] The variation in the serotonin and noradrenaline reuptake inhibition across TCAs may be a potential explanation for the differences in sedation and REM sleep suppression.[12]

The association between psychotropic medication and non-REM (NREM) sleep microstructure has been quantified using cyclic alternating pattern (CAP) analysis. CAP describes periodically recurring short increases (<60 s) in electroencephalography (EEG) activity in NREM stages, separated by lower-amplitude background periods.[13] Such short activation phases represent bursts of high frequency (A3), high amplitude (A1), or both (A2) as compared to normal cortical activity.[14] By definition, subtypes A2 and A3 correlate with arousals as previous studies have shown 95% of subtypes A3 and 62% of subtypes A2 meet the scoring requirements for arousals.[15] Due to the inclusion of periodicity and pre-arousal activation,[13,16] CAP extends the current arousal definition by the American Sleep Disorders Association[17] and is regarded as a marker of sleep instability.[18]

Previous studies of the impact of psychotropic drugs on sleep microstructure are limited to tightly controlled laboratory studies with small sample sizes recruited from clinical cases and focusing on middle-aged people. Moreover, previous studies focused mostly on benzodiazepines and nonbenzodiazepines, whereas the impact of other commonly used psychotropic drugs such as SSRI or TCA on CAP remains largely unknown. Benzodiazepine usage and CAP in people with chronic insomnia and situational insomnia have shown that the acute intake reduces the CAP rate and the number of A1 phases per hour of NREM sleep.[19-22] In a double-blind crossover study, the short-acting benzodiazepines brotizolam and triazolam significantly lowered CAP rate during situational insomnia, demonstrating their sleep protective effect.[21] In a similar study, the benzodiazepines lorazepam and triazolam caused a reduction in CAP rate, A1 phases and an increase in A2+A3 phases compared to placebo.[21] In the same study, the intake of the nonbenzodiazepine zolpidem resulted in the lowest CAP rate as well as a significant decrease in EEG arousals.[22] In a single-blinded study, six adult dysthymic patients with chronic insomnia treated with controlled-release trazodone showed a significantly decreased CAP time and CAP rate.[23]

The impact of psychotropic drugs on sleep microstructure in older individuals across larger population cohorts remains unknown. Hence, we analyzed the association of benzodiazepine or SSRI use with sleep macro- and microstructure in large community-based cohort studies of older people. In each study, we characterized CAP in groups treated with SSRIs or benzodiazepines ($n > 20$) in comparison to large groups with no psychotropic intake.

Methods

Study samples: MrOS and SOF

This study used data from two multi-center sleep cohorts Osteoporotic Fractures in Men (MrOS) Study and the Study of Osteoporotic Fractures (SOF). Both data sets were provided by the National Sleep Research Resource (available online at the National Sleep Research Resource; sleepdata.org),[24] and detailed individual drug usage was provided by the University of California San Francisco and California Pacific Medical Center Research Institute. MrOS is a multi-center, longitudinal, observational study examining the fracture risk in older men regarding skeletal, lifestyle, and medical factors.[25] In total, 5,994 community-dwelling men aged 65 and older were recruited at six clinical sites during baseline examination from 2000 to 2002 with the requirement that all participants needed to be able to walk without assistance and must not have had a bilateral hip replacement.[26] Between December 2003 and March 2005, 3,135 men who used no mechanical devices or oxygen during sleep enrolled into the MrOS Sleep Study, an ancillary sleep study of the MrOS cohort, for comprehensive overnight in-home polysomnography (PSG).[26] We removed recordings with technically inadequate PSG or fewer than 3 hours of good EEG quality resulting in 2,811 participants. Similar to the MrOS, the multisite, observational SOF studied risk factors for hip fractures among women aged 65 years and older with a follow-up starting between 1986 and 1988.[27] As part of the eighth clinic visit from 2002 to 2004, 461 women completed an unattended overnight in-home PSG to investigate the relationship of sleep disturbances to a range of health outcomes.[28,29] In alignment with the MrOS, we discarded recordings with technically inadequate PSG or fewer than three hours of good EEG quality resulting in 426 recordings.

Cyclic alternating pattern (CAP) analysis

CAP analysis was performed utilizing a fully automated CAP scoring system[30,31] according to the atlas and rules for scoring CAP.[13] A CAP sequence is defined as at least two consecutive CAP cycles terminated by an activation phase (A-phase) that was defined as non-CAP as it does not form a cycle. A CAP cycle comprises an A-phase representing a transient, phasic event in EEG activity followed by a background phase (B-phase) that separates two successive A-phases. Typical patterns for A-phases include delta bursts, vertex sharp transients, K-complex sequences, K-alpha, polyphasic bursts, intermittent alpha, and arousals.[14] A-phases were subdivided into periods of slow high-amplitude waves (A1), fast low-amplitude EEG rhythms (A3), or a mixture of both (A2).[14] CAP

sequences occur by definition only in NREM periods as REM sleep includes mainly desynchronized A-phases separated by a background period longer than 60s.[13] Hence, REM periods were removed from our CAP analysis and the cortical activity between two CAP sequences was considered non-CAP.

The fully automated CAP detection system contains a deep learning recurrent neural network trained on manually scored recordings from 15 healthy participants and 24 participants with sleep disorders from PhysioNet, a publicly available database.[32] The training recordings were conducted and visually scored by the Sleep Disorders Center of the Ospedale Maggiore of Parma, Italy. Our system reports a second-based sensitivity of 76% and an accuracy of 86% on 16 normal subjects and an inter-rater reliability, quantified by the Cohen's kappa coefficient, of 0.53 on 16 healthy participants and 0.56 on a set of 30 participants with nocturnal frontal lobe epilepsy. In comparison, human scorers achieved an A phase-based inter-rater reliability of 0.42 and 0.75.[33]

Here, we defined the CAP rate as the percentage of NREM sleep covered by CAP sequences. Subtype indices were defined as the number of A1 and A2 + A3, respectively, per hour of NREM sleep. Subtypes A2 and A3 were merged into a single parameter due to their congruent nature.

Spectral power analysis

In addition to CAP analysis, we conducted EEG power spectral analysis during NREM sleep. We calculated the power spectral density estimate using Welch's method on a 2-second sliding window with 50% overlap and Hamming windowing. Subsequently, the mean absolute power spectral density for five EEG frequency bands (delta 1-4 Hz; theta 4-8; alpha 8-12 Hz; sigma 12-15 Hz; beta 15-30 Hz) was computed by averaging across all NREM sleep epochs.

Psychotropic medication

We selected samples for our analysis according to the self-reported psychotropic medication usage and the psychotropic medication history based on the participant's prescription and non-prescription medications in MrOS and SOF. We examined the following classes of psychotropic drugs: benzodiazepine and SSRI. We excluded participants that reported the intake of more than one psychotropic drug class to avoid mixed effects in our analysis. Then, we grouped samples into the following medication classes: No medication, benzodiazepine, and SSRI. Participants using trazodone, TCA, zolpidem, or nonbenzo nonbarbituate sedative hypnotic were excluded

due to the small sample size in either one or in both studies (n < 5). A detailed medication list for each class of drugs is provided in Table S1 in the Supplemental Material.

Statistical methods

Prior to our analysis, we removed samples with no medical history or sleep architecture information reducing the number of samples to 2,657 in MrOS and 381 in SOF. All analyses were performed within the specific cohort study, either the MrOS or the SOF.

We applied the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables to assess differences in characteristics between the no medication group and each medication group in MrOS and SOF. We compared each medication group to the no medication group within each specific cohort and used post-hoc Bonferroni correction for all tests within a medication group to adjust probability values according to multiple testing correction. For each statistical test, the significance level for the adjusted P values was 0.05.

To further explore the association between psychotropic drug usage and CAP parameters, multivariable regression within each specific cohort adjusted for age, body mass index (BMI), the apnea-hypopnea index including all apneas (central and obstructive) and hypopneas with or without arousals associated with at least a >= 3% oxygen desaturation (AHI), self-reported health status, depression symptoms (Geriatric Depression Scale score), anxiety (Goldberg Anxiety Scale score), current smoking status, and medical history was conducted with drug usage as independent variable and CAP rate, A1 index, and A2+A3 index as the dependent variables. Medical history was categorized as: no selected medical conditions, 1-2 selected medical conditions, and >2 selected medical conditions, where selected medical conditions were stroke, coronary artery disease or myocardial infarction, congestive heart failure, hypertension, diabetes mellitus, Parkinson's Disease, dementia, Graves' disease, and chronic obstructive lung disease. Table S2 in the Supplemental Material details the frequencies of the listed selected medical conditions for each medication group in each specific cohort. The polysomnographic measures arousal index in NREM sleep (AI-NREM) and periodic limb movement in sleep index (PLMSI) were excluded as covariates under the assumption that they are associated with the between-subject factor drug usage and subsequently not independent of drug usage. We fitted a linear regression model for each dependent variable without drug usage as the independent variable and one model with drug usage as the independent variable. Afterwards, both models were compared using analysis of variance (ANOVA Type I) to

test the main effect of drug usage on CAP parameters while controlling for the effects of the previously listed variables. Regression coefficients were post-hoc standardized using their standard deviation.

Results

The median age of participants in the SOF sample was 82 years, and participants had a median BMI of 27.0 kg/m^2. The median scored sleep time was 352 min with a median percentage of sleep in stage N1, N2, N3, and REM of 4.4%, 54.9%, 19.7%, and 18.4%, respectively. Participants in the SOF sample experienced a median AI-NREM of 20.0/h and a median AHI of 11.7/h. The median PLMSI among the SOF sample was 21.9/h. Participants in the SOF sample had a median CAP rate of 54.3% with an A1 index of 13.8/h and an A2+3 index of 44.7/h.

In the MrOS sample, the median age of participants was 76 years, and participants had a median BMI of 26.7 kg/m^2. Participants in the MrOS sample slept a median percentage of sleep in stage N1, N2, N3, and REM of 6.0%, 62.8%, 10.0%, and 19.6%, respectively, with an overall scored median sleep time of 360 min. The median AI-NREM for participants in the MrOS sample was 22.4/h, the median AHI was 12.6/h, and the median PLMSI was 23.6/h. The median CAP rate in the MrOS sample was 57.2%, with an A1 index of 15.5/h and an A2+3 index of 46.5/h.

Table 1 lists the details of psychotropic drug usage, demographics, and health measures in MrOS and SOF. The percentage of participants reportedly using benzodiazepine was significantly higher in SOF than in MrOS. Moreover, the proportion of women using SSRIs was higher than that of men.

Association between psychotropic medication and sleep micro- and macrostructure

Table 2 details the distributions of sleep disturbances, CAP, and sleep architecture measures across sample groups using no medication, benzodiazepine, and SSRI in MrOS and SOF.

Association between psychotropic drug usage and sleep macrostructure

MrOS participants that reported using benzodiazepine had significantly altered AI-NREM, AHI, REM latency, and percentage of sleep in stage N2 as compared to the no medication group in MrOS (AI-NREM: 16.8 no./h (±17.2) vs. 22.4 no./h (±15.7), adjusted Mann-Whitney U P = 0.038; AHI: 7.2 no./h (±12.1) vs. 12.7 no./h (±17.9), adjusted Mann-Whitney U P = 0.016, REM latency: 72.0 min (±61.0) vs. 61.0 min (±34.0), adjusted Mann-Whitney U P =

0.013; Percentage of stage N2 sleep: 66.2% (±14.4) vs. 62.6% (±12.8), adjusted Mann-Whitney U adjusted P = 0.046). SOF participants using benzodiazepine showed sleep architecture and levels of disturbance similar to their respective no medication groups.

SSRI users in MrOS experienced a significantly prolonged sleep latency, and REM latency, as well as a significantly lower percentage of REM sleep as compared to participants in MrOS with no psychotropic medication intake (sleep latency: 25.0 min (±32.8) vs. 15.0 min (±19.5), adjusted Mann-Whitney U P = 0.008; REM latency: 124.0 min (±90.0) vs. 61.0 min (±34.0), adjusted Mann-Whitney U P < 0.001, Percentage of REM sleep: 17.1% (±8.9) vs. 19.7% (±8.6), adjusted Mann-Whitney U P < 0.001). In SOF, SSRI users had a significantly higher PLMSI, and a significantly lower percentage of REM sleep compared to SOF participants who did not use psychotropic medication (PLMSI: 54.7 no./h (59.7) vs. 18.4 no./h (50.8), adjusted Mann-Whitney U P = 0.018; Percentage of REM sleep: 17.1% (±8.9) vs. 19.7% (±8.6), adjusted Mann-Whitney U P = 0.003).

Association between psychotropic drug usage and sleep microstructure

With regards to sleep microstructure, MrOS participants using benzodiazepines showed a significantly lower A1 index, as well as a significantly higher sigma power as compared to no psychotropic medication users (A1 index: 5.5 no./h (±11.8) vs. 16.0 no./h (±20.6), adjusted Mann-Whitney U P < 0.001; sigma power: 2.5 μV^2 (±1.8) vs. 1.9 μV^2 (±1.3), adjusted Mann-Whitney U P < 0.001). CAP rate and A2+3 index were slightly altered in benzodiazepine users as compared to no psychotropic medication users in MrOS but did not reach statistical significance (CAP rate: P=0.145, A2+3 index: P=0.414). There were no significant alterations in CAP measures (P≥0.500 for all three CAP measures) for benzodiazepine users in SOF but a significantly higher sigma power (sigma power: 3.0 μV^2 (±1.6) vs. 2.2 μV^2 (±1.4), adjusted Mann-Whitney U P = 0.013) compared to no psychotropic medication users in SOF.

SSRI users in SOF had a significantly higher A2+3 index, and beta power in comparison to women who did not use psychotropic medication (A2+3 index: 69.3 no./h (±34.0) vs. 42.7 no./h (±32.5), adjusted Mann-Whitney U P = 0.003; beta power: 0.7 μV^2 (±0.3) vs. 0.5 μV^2 (±0.3), adjusted Mann-Whitney U P = 0.012). SSRI users had a slightly higher CAP rate as compared to no psychotropic medication users in SOF but it did not reach statistical significance (CAP rate: P=0.249). Additionally, no significant differences were found for A1 index between SSRI users and no psychotropic drug users in SOF (A1 index: P=1.000). There were no significant differences in CAP

measures (P=1.000 for all three CAP measures) but significantly higher beta power (beta power: 0.6 μV^2 (±0.5) vs. 0.5 μV^2 (±0.3), adjusted Mann-Whitney U P = 0.018) between SSRI users and no psychotropic drug users in the MrOS cohort.

Multivariable regression analysis

Tables 3 lists the standardized regression coefficents and ANOVA outcomes of the multivariable regression analysis assessing the main association between benzodiazepine and SSRI usage, respectively, in MrOS and SOF adjusted for age, BMI, AHI, self-reported health status, depression symptoms (Geriatric Depression Scale score), anxiety (Goldberg Anxiety Scale score), current smoking status, and medical history.

In MrOS, benzodiazepine usage was significantly associated with a lower CAP rate and A1 index, and a higher A2+3 index in the adjusted regression model (CAP rate: P=0.039, A1 index: P < 0.001, A2+3 index: P=0.009), whereas SSRI usage had no significant association with sleep microstructure. On the contrary, SSRI usage was significantly associated with higher CAP rate and A2+A3 index in SOF even after adjusting for multiple confounders (CAP rate: P=0.046, A2+3 index: P=0.004). Regarding benzodiazepine usage, a pattern similar to MrOS was observed in SOF indicated by the standardized regression coefficients (MrOS: β=-0.11, SOF: β=-0.10), but potentially limited by the smaller sample size (A1 index: P = 0.060).

Discussion

Our analysis suggests that SSRIs are significantly associated with sleep microstructure in community-dwelling women aged 79 or older, whereas benzodiazepines are significantly associated with sleep microstructure in community-dwelling men aged 67 or older. Our data suggest larger sleep continuity and lower sleep fragmentation in older men using benzodiazepine, indicated by a significantly lower CAP rate. A-phase subtype analysis revealed a significantly lower A1 index for benzodiazepine users, implying a reduction in synchronized sleep patterns. The multivariable regression analysis indicated a significant but weak association between benzodiazepine usage and the frequency of A2+3 phases. SSRI usage was not significantly associated with sleep microstructure in older men. However, SSRIs appeared to be associated with sleep instability in older women, as shown by a significantly higher PLMSI among SSRI users. The higher sleep fragmentation in SSRI users is supported by a significantly higher CAP rate and A2+3 index, suggesting less synchronized sleep. To the best of our knowledge, this is the first detailed analysis of the association between psychotropic drugs and sleep micro- and macrostructure in older men and women using a large sample of community-dwelling participants that were

not selected based on psychotropic drugs drug usage or sleep problems. The outcomes of our analysis are summarized in Table 4. Our results suggest that CAP analysis can help to enhance the current knowledge on sleep altering mechanisms induced by psychotropic drugs by identifying potential differences based on medication class.

Numerous studies on the effect of benzodiazepines on sleep have shown that benzodiazepines have a preserving effect on sleep continuity and efficiency.[7] In particular, in artificially created perturbing sleep environments simulating insomniac conditions, benzodiazepines significantly reduce the level of sleep fragmentation induced by acoustic perturbation, as shown by a significantly lowered CAP rate.[21,22] Our data corroborate previous findings that were mostly obtained in individuals with chronic insomnia or in situational insomnia on the reduction of CAP sequences associated with benzodiazepine usage, mainly supported by a significantly lower number of A1 subtypes. Although the reduction in CAP phases and slow-wave sleep patterns (A1 phases) among benzodiazepine users did not reach statistical significance in the cohort of older women possibly due to the limited sample size, smaller effect size, impact of sleep disorders, or older age in SOF, a similar direction was observed to that seen in the cohort of older men. Our data suggest that previous reports on the association of benzodiazepine and sleep microstructure translate to the broader population of older people with presumably fewer, milder insomnia symptoms.

The significantly lower AI-NREM and AHI as sleep disturbance measures supported the trend towards lower sleep fragmentation in MrOS participants using benzodiazepine. Previous studies on the effect of benzodiazepine usage on sleep apnea have reported only limiting or conflicting information. A placebo-controlled, double-blind study evaluating the influence of nitrazepam, a commonly prescribed benzodiazepine, on apnea frequency and severity reported no negative effect on sleep apnea in patients with mild to moderate sleep apnea.[36] Our results suggest no difference in clinical importance either as benzodiazepine users and the no medication group indicate mild sleep apnea symptoms, although benzodiazepine users had a lower AHI. EEG power spectra analysis revealed a significantly larger sigma activity for benzodiazepine users in both cohorts as compared to the respective no medication group but no significant differences in slow-wave activity. Sleep staging measures used in the clinical setting focussing on sleep architecture indicated a pattern towards slow-wave sleep (N3) reduction that did not reach statistical significance. Hence, CAP metrics were more sensitive than the conventional sleep staging method to the adverse impact of benzodiazepine on slow-wave activity.

Moreover, our results show a 10% higher PLMSI in the benzodiazepine group compared to the no medication group in the SOF cohort. This could be due to the significantly larger percentage of participants diagnosed with restless leg syndrome (RLS) or periodic limb movement disorder (PLMD) prior to the sleep visit in the benzodiazepine group as compared to the no medication group in SOF (benzodiazepine group: 18.5%, no medication group: 5.8%, P = 0.032).

Our results suggest that SSRI usage is adversely associated with sleep fragmentation in older women, particularly increasing periods with high EEG desynchrony and large high frequency EEG activity. We also report a significantly greater PLMSI in older women using SSRI compared to older women using no psychotropic medication, supporting the link of periodic limb movements to CAP sequences, notably A2 and A3 phases.[37] This corroborates previous findings on the association between SSRI and sleep disturbances in the same cohort, suggesting that SSRI use is associated with concurrent sleep disturbances, sleep fragmentation, and a greater high frequency EEG activity.[38,39] However, the significantly elevated PLMSI in older women using SSRI compared to older women using no psychotropic medication could potentially be an inherited bias due to the cross-sectional study design resulting in an under- or overestimate of the association of SSRI with periodic limb movements. A comparison of the number of participants reporting a diagnosis with RLS or PLMD prior to the PSG recording showed no significant differences between the SSRI group and the group using no psychotropic medication in SOF (no medcation: 5.8%, SSRI: 4.2%, P=1.000).

Interestingly, we did not observe the same disparity in older men. Besides the cross-sectional nature of the study, two additional factors could explain the lack of associations between CAP rate and SSRI usage when performing group comparisons. Most antidepressant agents activate the central nervous system and can therefore increase arousal instability (CAP) during sleep. Also, on average, PLMSI levels for the medication group were pathological (threshold 15/h), both in MrOS (23.4/h) and SOF (18.4/h) according to the International Classification of Sleep Disorders – Third Edition (ICSD-3) criteria. Although PLMSI was significantly larger in the SSRI usage group, especially in SOF (54.7/h), the CAP rate did not reach significance but was higher compared to no medication, coupled with a significant rise in A2+3 index. Multivariate regression analysis subsequently confirmed the significant association between CAP rate and SSRI usage in SOF.

It has been hypothesized that the A phases in CAP operate as time windows for the activation of the motor system resulting in periodic limb movements. The acute intake of SSRIs is a risk factor for RLS,[11] potentially due to associated hyperdopaminergic side effects.[40] Animal studies have shown that SSRI use causes not only elevated extracellular serotonin levels by inhibiting the serotonin uptake but can also lead to increased extracellular dopamine levels varying between SSRIs.[41,42] Potentially, the extracellular serotonin excess is uptaken by dopamine transporters into dopamine neurons in the brain striatum, inhibiting the uptake of dopamine.[43,44] Hence, sustained administration of SSRIs can lead to a decreased firing rate and burst activity of neuronal dopamine activity,[45] resulting in more periodic limb movements.

The differences in outcomes for the MrOS and the SOF on the association between SSRI and sleep microstructure may be explained by the gender variances in the association between SSRI drug usage and RLS[46] or maybe due to age or study design differences in the two cohorts. Fluoxetine has shown to be associated with RLS in women, whereas citalopram, paroxetine, and amitriptyline appear to be more strongly associated with RLS in men.[46] We

also tested for a potential higher usage of sleep medicine such as zolpidem, melatonin, trazodone, and acetaminophen in the male cohort that may have been used to counteract the effect of SSRI usage on sleep fragmentation, but the prevalence of sleep medicine usage was higher in SOF than in MrOS (MrOS: 13%, SOF: 25%, P<0.001). Our results suggest a need to further investigate potential age and gender differences in sleep responses to psychotropic medication, potentially due to different effective doses, pharmodynamics, or other factors. While we found sex differences in the associations of benzodiazepine and SSRI use with CAP parameters, characteristics such as age and health status between sexes may have contributed to these inconsistent findings.

A limitation of this study is the lack of information available on the dose, indication, frequency, time of administration, duration, and half-life of the psychotropic medication. As the indication for psychotropic drug use was not documented in the MrOS or the SOF, our results could not be adjusted to potential confounders caused by the underlying mental health diagnosis other than Parkinson's Disease, dementia, and mood disorders. Further, we excluded subjects that used multiple psychotropic drugs to eliminate confounding effects. Concommitant non-psychotropic drug treatment was not considered in our analysis. Moreover, we cannot exclude the possibility that participants who were prescribed psychotropic drugs had preexisting sleep problems or used other medication with possible impact on sleep such as beta-blockers, and antihistamine. Lastly, the CAP scoring produced by our automated detection system may not always concur with manual labelling. Although it has shown strong performance,[30] high reproducibility,[31] and utility for clinical research,[31,47,48] the output of the classification system depends on the human scoring in the training set, which is limited by significant inter-scorer variability. Fine tuning of the algorithm using the labels of a manually scored subset of the cohort is not feasible due to the tedious and time-consuming nature of scoring overnight recordings.

In conclusion, we show that sleep fragmentation is associated with benzodiazepine use in older men, and SSRI use in older women. SSRI use was associated with periodic limb movements in older women, potentially linked to a rise in desynchronized sleep patterns. Benzodiazepines promoted sleep continuity in older men, decreasing slow-wave sleep patterns. Our results highlight the importance of including CAP parameters to amend the understanding of differences in sleep-wake mechanisms based on psychotropic usage with possible future indications for psychiatric disorder treatment. With the need for more reliable sleep quality measures and quantification methods for sleep fragmentation and instability, additional enrichment to nocturnal wake bouts and sleep macrostructure can be provided by CAP parameters, including CAP rate (the objective measure of NREM sleep instability) and CAP-phase A subtypes (which incorporate and amplify the limited knowledge reflected by conventional EEG arousals). Diagnostic accuracy, drug effects and pre- vs. post-treatment comparisons may be improved should CAP metrics be routinely applied in clinical practice.

Abbreviations

AHI	apnea-hypopnea index
A-phase	activation phase
A1	slow high-amplitude electroencephalography rhythms
A2	mixture of slow and fast electroencephalography rhythms
A3	fast low-amplitude electroencephalography rhythms
B-phase	background phase
AI-NREM	arousal index in NREM sleep
BMI	body mass index
CAP	cylic alternating pattern
EEG	electroencephalography
ICSD-3	International Classification of Sleep Disorders – Third Edition
MrOS	Osteoporotic Fractures in Men Study
NREM	non-rapid eye movement
PLMSI	periodic limb movement in sleep index
PLMD	periodic limb movement disorder
PSG	polysomnograpy
REM	rapid eye movement
RLS	restless leg syndrome
SOF	Study of Osteoporotic Fractures
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
WASO	wake after sleep onset

References

1. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA. 1989;262(11):1479-1484. doi:10.1001/jama.1989.03430110069030

2. Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. J Psychiatr Res. 2003;37(1):9-15. doi:https://doi.org/10.1016/S0022-3956(02)00052-3

3. Doghramji K, Jangro WC. Adverse effects of psychotropic medications on sleep. Psychiatr Clin North Am. 2016;39(3):487-502. doi:https://doi.org/10.1016/j.psc.2016.04.009

4. Gottesmann C. GABA mechanisms and sleep. Neuroscience. 2002;111(2):231-239. doi:https://doi.org/10.1016/S0306-4522(02)00034-9

5. Plante DT. The evolving nexus of sleep and depression. Am J Psychiatry. 2021;178(10):896-902. doi:10.1176/appi.ajp.2021.21080821

6. Wichniak A, Wierzbicka A, Walęcka M, Jernajczyk W. Effects of antidepressants on sleep. Curr Psychiatry Rep. 2017;19(9):63. doi:10.1007/s11920-017-0816-4

7. Morin CM, Daley M, Ouellet M-C. Insomnia in adults. Curr Treat Options Neurol. 2001;3(1):9-18. doi:10.1007/s11940-001-0020-y

8. Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds III CF, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. JAMA. 1997;278(24):2170-2177. doi:10.1001/jama.1997.03550240060035

9. Bossini L, Casolaro I, Koukouna D, Cecchini F, Fagiolini A. Off-label uses of trazodone: a review. Expert Opin Pharmacother. 2012;13(12):1707-1717. doi:10.1517/14656566.2012.699523

10. Abad VC, Guilleminault C. Sleep and psychiatry. Dialogues Clin Neurosci. 2005;7(4):291-303. doi:10.31887/DCNS.2005.7.4/vabad

11. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. J Psychosom Res. 2002;53(1):547-554. doi:https://doi.org/10.1016/S0022-3999(02)00443-9

12. Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. Hum Psychopharmacol Clin Exp. 2005;20(8):533-559. doi:https://doi.org/10.1002/hup.726

13. Terzano MG, Parrino L, Sherieri A, et al. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. Sleep Med. 2001;2(6):537-553.

14. Terzano MG, Parrino L. Origin and significance of the cyclic alternating pattern (CAP). Sleep Med Rev. 2000;4(1):101-123.

15. Parrino L, Smerieri A, Rossi M, Terzano MG. Relationship of Slow and Rapid EEG Components of CAP to ASDA Arousals in Normal Sleep. Sleep. 2001;24(8):881-885. doi:10.1093/sleep/24.8.881

16. Hartmann S, Ferri R, Bruni O, Baumert M. Causality of cortical and cardiovascular activity during cyclic alternating pattern in non-rapid eye movement sleep. Philos Trans R Soc A Math Phys Eng Sci. 2021;379(2212):20200248. doi:10.1098/rsta.2020.0248

17. ASDA. EEG Arousals: Scoring Rules and Examples. Sleep. 1992;15(2):173. doi:10.1093/sleep/15.2.173

18. Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instability. Sleep Med Rev. 2012;16(1):27-45. doi:10.1016/j.smrv.2011.02.003

19. Mazza M, Losurdo A, Testani E, et al. Polysomnographic findings in a cohort of chronic insomnia patients with benzodiazepine abuse. J Clin Sleep Med. 2014;10(01):35-42.

20. Manconi M, Ferri R, Miano S, et al. Sleep architecture in insomniacs with severe benzodiazepine abuse. Clin Neurophysiol. 2017;128(6):875-881. doi:https://doi.org/10.1016/j.clinph.2017.03.009

21. Terzano MG, Parrino L, Boselli M, Dell'Orso S, Moroni M, Spaggiari MC. Changes of cyclic alternating pattern (CAP) parameters in situational insomnia under brotizolam and triazolam. Psychopharmacology (Berl). 1995;120(3):237-243. doi:10.1007/BF02311169

22. Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG. Multidrug comparison (lorazepam, triazolam, zolpidem, and zopiclone) in situational insomnia: polysomnographic analysis by means of the cyclic alternating pattern. Clin Neuropharmacol. 1997;20(3).

23. Parrino L, Spaggiari MC, Boselli M, Di Giovanni G, Terzano MG. Clinical and polysomnographic effects of trazodone CR in chronic insomnia associated with dysthymia. Psychopharmacology (Berl). 1994;116(4):389-395. doi:10.1007/BF02247467

24. Dean II DA, Goldberger AL, Mueller R, et al. Scaling up scientific discovery in sleep medicine: the National Sleep Research Resource. Sleep. 2016;39(5):1151-1164. doi:10.5665/sleep.5774

25. Orwoll E, Blank JB, Barrett-Connor E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study — A large observational study of the determinants of fracture in older men. Contemp Clin Trials. 2005;26(5):569-585. doi:10.1016/j.cct.2005.05.006

26. Blackwell T, Yaffe K, Ancoli-Israel S, et al. Associations between sleep architecture and sleep-disordered breathing and cognition in older community-dwelling men: the Osteoporotic Fractures in Men Sleep Study. J Am Geriatr Soc. 2011;59(12):2217-2225. doi:10.1111/j.1532-5415.2011.03731.x

27. Cummings SR, Black DM, Nevitt MC, et al. Appendicular bone density and age predict hip fracture in Women. JAMA. 1990;263(5):665-668. doi:10.1001/jama.1990.03440050059033

28. Spira AP, Blackwell T, Stone KL, et al. Sleep-disordered breathing and cognition in older women. J Am Geriatr Soc. 2008;56(1):45-50. doi:10.1111/j.1532-5415.2007.01506.x

29. Claman DM, Redline S, Blackwell T, et al. Prevalence and correlates of periodic limb movements in older women. J Clin Sleep Med. 2006;2(04):438-445.

30. Hartmann S, Baumert M. Automatic A-phase detection of cyclic alternating patterns in sleep using dynamic temporal information. IEEE Trans Neural Syst Rehabil Eng. 2019;27(9):1695-1703. doi:10.1109/TNSRE.2019.2934828

31. Hartmann S, Bruni O, Ferri R, Redline S, Baumert M. Characterization of cyclic alternating pattern during sleep in older men and women using large population studies. Sleep. 2020;43(7). doi:10.1093/sleep/zsaa016

32. Goldberger AL, Amaral LAN, Glass L, et al. PhysioBank, PhysioToolkit, and PhysioNet. Circulation. 2000;101(23):e215 LP-e220.

33. Ferri R, Bruni O, Miano S, Smerieri A, Spruyt K, Terzano MG. Inter-rater reliability of sleep cyclic alternating pattern (CAP) scoring and validation of a new computer-assisted CAP scoring method. Clin Neurophysiol. 2005;116(3):696-707. doi:10.1016/j.clinph.2004.09.021

34. Baker FM, Espino D V. A Spanish version of the geriatric depression scale in Mexican-American elders. Int J Geriatr Psychiatry. 1997;12(1):21-25. doi:https://doi.org/10.1002/(SICI)1099-1166(199701)12:1<21::AID-GPS444>3.0.CO;2-2

35. Goldberg D, Bridges K, Duncan-Jones P, Grayson D. Detecting anxiety and depression in general medical settings. Br Med J. 1988;297(6653):897-899.

36. Hoijer U, Hedner J, Ejnell H, Grunstein R, Odelberg E, Elam M. Nitrazepam in patients with sleep apnoea: a double-blind placebo-controlled study. Eur Respir J. 1994;7(11):2011 LP - 2015.

37. Parrino L, Boselli M, Buccino GP, Spaggiari MC, Di Giovanni G, Terzano MG. The cyclic alternating pattern plays a gate-control on periodic limb movements during non-rapid eye movement sleep. J Clin Neurophysiol. 1996;13(4).

38. Ensrud KE, Blackwell TL, Ancoli-Israel S, et al. Use of selective serotonin reuptake inhibitors and sleep disturbances in community-dwelling older women. J Am Geriatr Soc. 2006;54(10):1508-1515. doi:https://doi.org/10.1111/j.1532-5415.2006.00880.x

39. Feige B, Voderholzer U, Riemann D, Dittmann R, Hohagen F, Berger M. Fluoxetine and Sleep EEG: Effects of a Single Dose, Subchronic Treatment, and Discontinuation in Healthy Subjects. Neuropsychopharmacology. 2002;26(2):246-258. doi:10.1016/S0893-133X(01)00314-1

40. Nader P, Coralie L, Baleydier B, Andrei C, Susanne M, Damsa C. Restless legs syndrome induced by citalopram: a psychiatric emergency? Gen Hosp Psychiatry. 2007;29(1):72-74. doi:https://doi.org/10.1016/j.genhosppsych.2006.10.006

41. Nakayama K. Effect of paroxetine on extracellular serotonin and dopamine levels in the prefrontal cortex. Naunyn Schmiedebergs Arch Pharmacol. 2002;365(2):102-105. doi:10.1007/s00210-001-0497-7

42. Bymaster FP, Zhang W, Carter PA, et al. Fluoxetine, but not other selective serotonin uptake inhibitors, increases norepinephrine and dopamine extracellular levels in prefrontal cortex. Psychopharmacology (Berl). 2002;160(4):353-361. doi:10.1007/s00213-001-0986-x

43. Zhou FC, Lesch K-P, Murphy DL. Serotonin uptake into dopamine neurons via dopamine transporters: a compensatory alternative. Brain Res. 2002;942(1):109-119. doi:https://doi.org/10.1016/S0006-8993(02)02709-9

44. Zhou F-M, Liang Y, Salas R, Zhang L, De Biasi M, Dani JA. Corelease of dopamine and serotonin from striatal dopamine terminals. Neuron. 2005;46(1):65-74. doi:https://doi.org/10.1016/j.neuron.2005.02.010

45. Dremencov E, El Mansari M, Blier P. Effects of sustained serotonin reuptake inhibition on the firing of dopamine neurons in the rat ventral tegmental area. J Psychiatry Neurosci. 2009;34(3):223-229. https://pubmed.ncbi.nlm.nih.gov/19448853

46. Baughman KR, Bourguet CC, Ober SK. Gender differences in the association between antidepressant use and restless legs syndrome. Mov Disord. 2009;24(7):1054-1059. doi:https://doi.org/10.1002/mds.22517

47. Hartmann S, Bruni O, Ferri R, Redline S, Baumert M. Cyclic alternating pattern in children with obstructive sleep apnea and its relationship with adenotonsillectomy, behavior, cognition, and quality of life. Sleep. 2021;44(1). doi:10.1093/sleep/zsaa145

48. DelRosso LM, Hartmann S, Baumert M, Bruni O, Ruth C, Ferri R. Non-REM sleep instability in children with restless sleep disorder. Sleep Med. 2020;75:276-281. doi:https://doi.org/10.1016/j.sleep.2020.07.033

Table 1: Distributions of demographic and health measures across MrOS and SOF

	MrOS			SOF		
	No medication	**Benzodiazepine**	**SSRI**	**No medication**	**Benzodiazepine**	**SSRI**
N	2,489	85	83	330	27	24
Demographic measures						
Age, years	76.0 (8.0)	77.0 (11.0)	76.0 (8.0)	82.0 (4.0)	83.0 (3.5)	84.0 (3.0)
BMI, kg/m^2	26.7 (4.7)	26.8 (5.8)	27.4 (4.2)	26.9 (6.2)	27.5 (6.2)	26.7 (7.0)
Health measures						
Current smoker	48 (1.9%)	2 (2.4%)	0 (0.0%)	5 (1.5%)	0 (0.0%)	0 (0.0%)
History of no selected medical conditions[#]	845 (33.9%)	17 (20.0%)	19 (22.9%)	88 (26.7%)	6 (22.2%)	3 (12.5%)
History of 1-2 selected medical conditions[#]	1,386 (55.7%)	48 (56.5%)	50 (60.2%)	196 (59.4%)	14 (51.9%)	12 (50.0%)
History of >2 selected medical conditions[#]	258 (10.4%)	**20 (23.5%)***	14 (16.9%)	46 (13.9%)	7 (25.9%)	9 (37.5%)
Self-reported health status, poor or very poor	24 (1.0%)	3 (3.5%)	1 (1.2%)	4 (1.2%)	1 (3.7%)	2 (8.3%)
Self-reported health status, fair	258 (10.4%)	16 (18.8%)	**20 (24.1%)***	65 (19.7%)	5 (18.5%)	7 (29.2%)
Self-reported health status, good or excellent	2,206 (88.6%)	**66 (77.6%)***	**62 (74.7%)***	261 (79.1%)	21 (77.8%)	15 (62.5%)
Depression symptoms						
Geriatric Depression Scale score, range 0-15	1.0 (2.0)	**2.0 (2.0)***	**2.0 (3.5)***	1.0 (3.0)	2.0 (2.5)	2.5 (3.3)
Geriatric Depression Scale score > 4[&]	181 (7.3%)	**18 (21.2%)***	**21 (25.3%)***	44 (13.3%)	6 (22.2%)	7 (29.2%)
Anxiety						
Goldberg Anxiety Scale score, range 0-9	0.0 (2.0)	**1.0 (4.0)***	**2.0 (4.0)***	0.0 (1.0)	1.0 (4.5)	1.0 (5.3)
Goldberg Anxiety Scale score > 4[$]	148 (5.9%)	**19 (22.4%)***	**14 (16.9%)***	51 (15.5%)	10 (37.0%)	8 (33.3%)

All values are presented as median ± interquartile range (IQR), or as frequencies (percentage).

[#] Selected medical conditions: stroke, coronary artery disease or myocardial infarction, congestive heart failure, hypertension, diabetes mellitus, Parkinson's Disease, dementia, Graves' disease, and chronic obstructive lung disease.

[&] A Geriatric Depression Scale score of 5 or higher is suggestive of depression[34]

[$] Patients with a Goldberg Anxiety Scale score > 4 have a 50% or higher chance of having a clinically important disturbance[35]

* Each medication group was compared with the no medication group within each specific cohort. All tests within each medication group were post-hoc Bonferroni corrected. Significance level for Bonferroni adjusted P values: $P < 0.05$

Table 2: Distributions of sleep disturbance, CAP, and polysomnographic measures across sample groups using no medication, benzodiazepine, SSRI, trazodone, and tricyclic antidepressants in MrOS and SOF

	MrOS			SOF		
	No medication	**Benzodiazepine**	**SSRI**	**No medication**	**Benzodiazepine**	**SSRI**
N	2,489	85	83	330	27	24
Sleep disturbance measures						
AI-NREM, no./h	22.4 (15.7)	**16.8 (17.2)***	25.3 (12.8)	19.4 (15.4)	20.7 (12.5)	26.8 (19.7)
AHI at >= 3% oxygen desaturation, no./h	12.7 (17.9)	**7.2 (12.1)***	15.6 (26.1)	10.7 (15.3)	13.3 (12.3)	16.7 (24.5)
PLMSI, no./h	23.4 (51.9)	26.1 (57.5)	33.5 (58.2)	18.4 (50.8)	28.4 (48.5)	**54.7 (59.7)***
CAP measures						
CAP rate, %	57.5 (21.2)	52.1 (22.7)	58.2 (17.4)	54.0 (26.1)	50.0 (20.1)	62.7 (22.1)
A1 index, no./h	16.0 (20.6)	**5.5 (11.8)***	15.4 (19.4)	14.3 (18.4)	9.0 (12.9)	8.7 (21.0)
A2+3 index, no./h	46.2 (31.3)	51.1 (25.9)	48.5 (29.7)	42.7 (32.5)	52.0 (27.4)	**69.3 (34.0)***
Sleep architecture measures						
Sleep latency, min	15.0 (19.5)	15.0 (37.0)	**25.0 (32.8)***	14.0 (31.8)	20.0 (34.5)	21.5 (46.0)
REM latency, min	61.0 (34.0)	**72.0 (61.0)***	**124.0 (90.0)***	64.0 (38.5)	62.0 (64.0)	140.0 (126.8)
Scored sleep time, min	359.0 (82.0)	351.0 (110.0)	379.0 (75.5)	356.0 (88.0)	352.0 (97.0)	320.0 (81.3)
Percentage of sleep in stage 1, %	6.0 (4.6)	5.7 (6.3)	6.3 (3.7)	4.3 (3.7)	4.4 (3.0)	5.0 (3.6)
Percentage of sleep in stage 2, %	62.6 (12.8)	**66.2 (14.4)***	66.0 (14.9)	54.3 (15.8)	58.4 (11.7)	62.2 (24.5)
Percentage of sleep in stage 3, %	10.1 (12.9)	7.1 (15.1)	9.5 (11.8)	20.4 (16.6)	12.8 (17.0)	15.4 (18.7)
Percentage of sleep in REM, %	19.7 (8.6)	17.1 (9.5)	**17.1 (8.9)***	18.8 (9.6)	21.3 (8.9)	**13.1 (10.9)***
Spectral power density measures						
Delta, μV^2	16.5 (9.8)	14.5 (9.2)	15.5 (12.4)	21.7 (11.5)	19.5 (7.9)	25.3 (16.2)
Theta, μV^2	5.3 (3.4)	5.2 (4.4)	5.5 (4.2)	7.6 (4.8)	6.6 (4.5)	9.8 (4.4)
Alpha, μV^2	4.2 (3.0)	4.8 (3.7)	3.7 (3.6)	5.5 (3.7)	7.0 (3.3)	5.4 (3.5)
Sigma, μV^2	1.9 (1.3)	**2.5 (1.8)***	1.9 (1.5)	2.2 (1.4)	**3.0 (1.6)***	2.3 (1.4)
Beta, μV^2	0.5 (0.3)	0.6 (0.3)	**0.6 (0.5)***	0.5 (0.3)	0.6 (0.2)	**0.7 (0.3)***

All values are presented as median (IQR), or as frequencies (percentage). AI-NREM, Non-rapid eye movement sleep (NREM) Arousal Index; AHI, Apnea-hypopnea Index; PLMSI, Number of Periodic limb movement (PLM) per hour of non-rapid eye movement sleep (NREM); REM, rapid eye movement.

* Each medication group was compared with the no medication group within each specific cohort. All tests within each medication group were post-hoc Bonferroni corrected. Significance level for Bonferroni adjusted P values: $P < 0.05$

Table 3: The association between drug usage and CAP parameters in MrOS and SOF assessed by multivariable regression analysis adjusted for age, BMI, AHI, self-reported health, depression symptoms, anxiety, current smoking status, and medical history.

	MrOS						SOF					
	Benzodiazepine			SSRI			Benzodiazepine			SSRI		
		Anova			Anova			Anova			Anova	
	β	F	P value	β	F	P value	β	F	P value	β	F	P value
CAP rate	-0.04	4.96	**0.039***	0.02	1.32	0.312	-0.02	0.19	0.646	0.11	4.46	**0.046***
A1 index	-0.11	**32.95**	**< 0.001***	-0.01	0.32	0.620	-0.10	3.60	0.060	-0.06	1.45	0.245
A2+3 index	0.05	**5.93**	**0.009***	0.02	1.36	0.299	0.06	1.29	0.264	0.16	**9.35**	**0.004***

* Significance level for P values: P < 0.05

Table 4: Summary of significant associations between psychotropic drug usage and sleep micro- and macrostructure

	Benzodiazepine	**SSRI**
MrOS (N= 2,657)	Lower number of arousals per hour Lower ratio of CAP sequences to NREM sleep Lower number of A1 phases per hour of NREM sleep Larger number of A2+3 phases per hour of NREM sleep Prolonged REM latency Prolonged time in stage N2	Prolonged sleep latency Prolonged REM latency Prolonged time in stage N2 Shortened time in REM
SOF (N= 381)	-	Larger number of periodic limb movement per hour Larger ratio of CAP sequences to NREM sleep Larger number of A2+3 phases per hour of NREM sleep Prolonged REM latency Shortened time in REM