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Class-specific and cumulative effects of psychotropic medication on sleep architecture: a polysomnographic retrospective study

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ABSTRACT

Objective: This study aims to investigate the impact of psychotropic medication interactions on sleep architecture. With the growing use of psychotropics, including antidepressants, antipsychotics, and mood stabilizers, this research seeks to understand how these drugs and their cumulative burden may affect key sleep parameters.
Material and methods: This retrospective study analyzed 60 non-psychotropic medication users, as well as 61 psychotropic medication users who underwent hospital polysomnography and met all inclusion criteria. Socio-demographic and polysomnographic data were obtained from a sleep laboratory database, between January 2018 and December 2021. Statistical analysis included normality assessment and appropriate parametric or non-parametric tests for group comparisons. Multivariable general linear models adjusted for age, sex, and BMI with HC3 robust errors evaluated associations. Cumulative psychotropic burden was analyzed as a continuous predictor.
Results: Medicated individuals exhibited reduced sleep efficiency ($p = .001$), prolonged sleep onset and REM latency ($p = .001$), increased light sleep, and fewer sleep cycles. Multivariable analyses showed antidepressants markedly increased REM latency ($p = .001$) and periodic limb movements ($p = .015$), while anticonvulsants enhanced slow-wave sleep ($p = .013$) and antipsychotics reduced arousals ($p = .004$). A dose–response relationship was observed, with greater psychotropic burden independently associated with longer REM latency ($p = .029$) and reduced arousal index ($p = .001$).
Conclusion: Psychotropic medications alter sleep architecture in recognizably class-specific ways, and these effects compound as the number of concurrent agents grows. Clinically, this argues for treating total psychotropic burden as a relevant variable in the interpretation of polysomnography, and underscores the need for prospective studies that account for dosage, serum levels, and cognitive outcomes.

What is known about this subject

- Psychotropic medications are widely used and are known to influence sleep architecture.
- Antidepressants and other central nervous system agents can alter REM sleep and sleep continuity.
- Drug interactions may further modify sleep patterns, but their combined effects remain insufficiently characterized.

What this study adds

- This study demonstrates that psychotropic drug interactions significantly impact multiple domains of sleep architecture.

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- Antidepressants were associated with increased REM latency and periodic limb movements, while anticonvulsants enhanced slow-wave sleep.
- These findings highlight the importance of considering drug interactions when evaluating patient well-being and potential sleep disturbances.

Principal Investigator statement

The authors confirm that the Principal Investigator for this paper is Daniel Alfaiate and that he had direct clinical responsibility for the patients.

1. Introduction

Psychotropic medication use has risen markedly in recent decades, extending beyond approved indications to off-label prescribing. This reflects greater recognition of mental disorders and increasing multimorbidity in aging populations, contributing to higher rates of polypharmacy and overall drug consumption globally (Health at a Glance, 2023, 2023).

According to the latest data from the Organization for Economic Cooperation and Development (OECD), antidepressant use increased by nearly 50% across member countries between 2011 and 2021. Although this may reflect an increased burden of mental ill-health, it also points to improved diagnostic practices, evolving treatment guidelines, and extended durations of medication use (Health at a Glance, 2023, 2023).

However, the expanding use of psychotropic medications raises critical concerns regarding their effects on sleep architecture. In addition to the individual effects of each medication, drug interactions are often underestimated and understudied. Beyond the effects of individual agents, the cumulative pharmacodynamic impact of concurrent psychotropic exposure on sleep architecture remains poorly characterised (Hartmann et al., 2023). Polypharmacy may amplify the sleep-disruptive burden of each agent in a combined regimen, yet this phenomenon is understudied relative to its clinical prevalence (Hartmann et al., 2023), (Ghossoub et al., 2021). Antidepressants, antipsychotics, anxiolytics, and mood stabilizers have all been shown to significantly alter various stages of sleep. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), for instance, commonly suppress rapid eye movement (REM) sleep and can prolong REM latency (Ghossoub et al., 2021) Certain antipsychotics and benzodiazepines, while enhancing total sleep time, can reduce slow-wave sleep (SWS), which is crucial for restorative rest. Moreover, some psychotropics, particularly antidepressants like mirtazapine and tricyclic antidepressants, have been associated with an increased incidence of periodic limb movements during sleep (PLMS), which may further disrupt sleep continuity (Kolla et al., 2018). Clinicians should be cognizant that certain antidepressants have the potential to exacerbate or precipitate primary sleep disorders, including restless legs syndrome, sleep bruxism, REM sleep behavior disorder, nightmares, and sleep apnea—some of which may be mediated through antidepressant-associated weight gain (Wichniak et al., 2017), (Lassale et al., 2024). Pharmacological effects on sleep microstructure are often underestimated in clinical settings, yet they have meaningful implications for both the short- and long-term well-being of patients. Data from large population-based cohorts suggest that benzodiazepines and selective serotonin reuptake inhibitors are linked to measurable changes in cyclic alternating pattern (CAP) metrics and NREM sigma activity. However, these observations are currently limited to these two commonly prescribed psychotropic classes. Consistently, a systematic review of benzodiazepines reports recurrent alterations in sleep stage distribution and NREM structure. Overall, current recent evidence on drug-related modifications of sleep architecture remains largely centered on benzodiazepines (Hartmann et al., 2023), (de Mendonça et al., 2023).

This study aims to provide a more nuanced understanding of the interaction between psychotropic drugs and sleep structure and evaluate how their probable cumulative burden impacts sleep. Focusing on polysomnography (PSG) data, being the gold standard for evaluating sleep architecture, therefore playing a critical role in identifying unintended adverse effects and consequently allowing treatment optimization strategies.

2. Material and methods

2.1. Study design

This was a retrospective study conducted among 61 individuals under psychotropic medication, being followed in the hospital psychiatry outpatient clinic, and 60 individuals not receiving psychotropic medication or any other medication affecting the central nervous system. The psychotropic cohort included patients with depressive disorders, anxiety disorders, bipolar disorders, personality disorders, adjustment disorder, schizoaffective disorder, and somatization disorder. Diagnostic categories were not mutually exclusive, as some patients presented psychiatric comorbidities. The median duration of psychiatric illness was 3 years (IQR 2–7 years). Detailed clinical characteristics of the psychotropic cohort are presented in Table 1.

No formal priori sample size calculation was performed, as this was a retrospective observational study based on available clinical records. The sample comprised all consecutive eligible individuals who underwent Type I in-laboratory PSG in the Sleep Laboratory of the Médio Tejo Local Health Unit between January 2018 and December 2021 and met the predefined inclusion and exclusion criteria. The control group sample consisted of patients who had been evaluated by a hospital physician and referred for Type I in-laboratory PSG due to excessive daytime sleepiness as their primary complaint, without other reported symptoms or comorbidities. All Individuals underwent polysomnography (PSG) at the Sleep Laboratory of Médio Tejo Local Health Unit, Torres Novas, Portugal between January of 2018 and December 2021. Drawing controls from the same clinical environment meant that both groups were subject to the same referral pathway, recording conditions, and scoring criteria, removing procedural variability as a source of noise. The sleep efficiency threshold applied to controls was a

Table 1
Clinical characteristics of the psychotropic medication group.

Psychiatric diagnosis	n	%
Depressive disorders	38	62.3
Anxiety disorders	15	24.6
Bipolar disorders	3	4.9
Personality disorders	3	4.9
Schizoaffective disorder	2	3.3
Adjustment disorder	2	3.3
Insomnia disorder	3	4.9
Somatization disorder	1	1.6

deliberate step to exclude individuals with likely undetected sleep pathology — not an arbitrary asymmetry, but a measure aimed at producing a cleaner comparison.

2.2. Data collection

Patients' medical records were analyzed and demographic data (gender, age, body mass index (BMI) Epworth Sleepiness Scale (ESS)), psychotropic medication, sleep efficiency, total sleep time, sleep latency, total sleep stages (N1, N2, N3, REM), wake after sleep onset (WASO), arousal index, number of sleep cycles, alpha-delta sleep, mean oxygen saturation were collected.

Patients younger than 18 years and older than 65 years, with diagnosed sleep disorder or illness that may interfere with sleep, pregnancy, breast feeding, individuals under non-invasive ventilation (NIV) during PSG or at home, history of stroke and diabetes, under medication or substance in quantities that interfere with sleep, recent history of drug or substance abuse were excluded from the study. With regard to the psychotropic group, participants who had been taking psychotropics irregularly, who had changed the dosage or type of medication less than three months previously, with an unstable diagnosis of psychiatric disorders, were excluded. Regarding the non-psychotropic group, individuals with mental illness diagnose, use of psychotropics and sleep efficiency under 85% were excluded.

2.3. Polysomnography protocol

Signal acquisition involved recording Type I in-laboratory PSG recommended channels: electroencephalogram, electrooculogram, electromyogram, electrocardiogram, oronasal flow, snoring, thoracoabdominal movements, arterial oxygen saturation, body position and video recording. The polysomnography and analysis software used included Embla N7000® and Alice 6® for signal acquisition, as well as Remlogic® and Sleepware G3®. PSG monitoring and the subsequent scoring and analysis of polysomnographic recordings were conducted according to the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events, using the version in effect at the time each recording was analyzed. All recordings were scored by highly experienced sleep technologists certified by the European Sleep Research Society (Berry et al., 2017), (Berry et al., 2018), (Berry et al., 2020).

2.4. Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Centro Hospitalar do Médio Tejo ethics committee number 24/DC/CA) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

2.5. Statistical analysis

Continuous variables were assessed for distributional normality using graphical inspection and appropriate statistical tests. Normally distributed variables are presented as mean and 95% confidence interval (CI), whereas non-normally distributed variables are expressed as median and 95% CI. Categorical variables are reported as absolute and relative frequencies.

Between-group comparisons (control vs psychotropic group) were performed using the independent samples Student's t-test or Mann–Whitney *U* test, as appropriate. Categorical variables were compared using Pearson's chi-square or Fisher's exact test.

To evaluate the independent associations between psychotropic drug classes and sleep outcomes, multivariable general linear models (GLM) with Type III sums of squares were constructed. All models were adjusted for age, sex, and body mass index (BMI). Robust standard errors were calculated using the HC3 estimator to account for potential heteroscedasticity. Adjusted mean differences (β coefficients) with 95% confidence intervals were reported.

Given the frequency of polypharmacy, a secondary analysis restricted to the psychotropic group was conducted to examine the cumulative effect of the number of psychotropic drug classes. In these models, the number of classes was treated as a continuous predictor, adjusted for age, sex, and BMI.

All predefined sleep architecture, continuity, respiratory, and subjective outcomes were evaluated in the multivariable framework. For clarity of presentation, only statistically significant associations are reported in the main tables; full model outputs are available upon request.

All statistical tests were two-sided, and statistical significance was defined as $p < 0.05$. Analyses were conducted using SPSS© (version 26).

3. Results

3.1. Sample characteristics

A total of 121 patients were included in the analysis, comprising 60 individuals in the control group and 61 in the psychotropic medication group. Baseline characteristics are presented in Table 2.

Patients receiving psychotropic medication were significantly older and had higher body mass index values compared with controls. Despite similar sex distribution between groups, relevant differences were observed in several sleep parameters at the unadjusted level. The psychotropic group demonstrated lower sleep efficiency, longer sleep onset latency, increased proportion of light sleep (N1+N2), markedly prolonged REM latency, and fewer sleep cycles. Mean nocturnal oxygen saturation was also modestly lower in medicated patients. No significant

Table 2
Baseline characteristics (control vs psychotropic group).

Variable	Control (n = 60)	Psychotropic (n = 61)	p-value
Demographic variables			
Age (years), mean ± 95% CI	40.3 [37.3–43.4]	48.1 [45.4–50.8]	0.001
BMI (kg/m^2), median [95% CI]	25.6 [24.1–27.2]	28.4 [28.0–30.9]	0.009
Male sex, n (%)	18 (30%)	13 (21.3%)	0.274
Subjective sleep			
ESS, median [95% CI]	9.5 [8.0–13.0]	8.0 [6.0–12.0]	0.013
Sleep architecture			
Sleep efficiency (%)	92.0 [91.1–92.8]	86.1 [82.8–89.4]	0.001
Sleep onset latency (min)	6.9 [5.0–9.5]	12.5 [9.5–17.4]	0.006
N1+N2 (%)	61.8 [60.3–65.2]	65.5 [62.4–69.8]	0.033
N3 (%)	19.0 [17.4–20.5]	18.0 [16.9–20.1]	0.254
REM latency (min)	84.3 [76.0–99.5]	143.0 [114.0–162.0]	0.001
REM sleep (%)	17.7 [16.9–19.3]	17.3 [15.1–19.4]	0.152
Sleep cycles (n)	4 [4–5]	3 [3–4]	0.001
Sleep continuity			
WASO (min)	28.0 [22.5–32.5]	26.5 [20.5–38.5]	0.983
Arousal index (n/h)	9.15 [7.6–10.2]	8.2 [6.7–9.9]	0.471
PLM index (n/h)	0.5 [0.0–0.8]	0.2 [0.0–2.5]	0.301
Respiratory parameters			
Mean SpO_2 (%)	96.0 [96.0–97.0]	95.2 [95.0–96.0]	0.003

BMI body mass index, *ESS* Epworth sleepiness scale, *N1+N2* non rapid eye movement light sleep, *N3* non rapid eye movement slow wave sleep, *REM* rapid eye movement sleep, *WASO* wake after sleep onset, *PLM* periodic leg movement, *SpO2* peripheral arterial oxygen saturation.

between-group differences were observed for N3 percentage, REM sleep percentage, WASO, Arousal index, or PLM index at the descriptive level.

3.2. Distribution of psychotropic burden

Among the 61 patients receiving psychotropic medication, polypharmacy was frequent (Table 3).

Only 29.5% were on monotherapy, whereas 34.4% were treated with two classes and 36.1% with three classes. Given this distribution, both class-specific and cumulative burden analyses were performed.

3.3. Adjusted associations between psychotropic drug classes and sleep architecture

Multivariable general linear models adjusted for age, sex, and BMI are shown in Table 4.

3.4. REM regulation

Antidepressant use was independently associated with a substantial prolongation of REM latency and a reduction in the number of sleep cycles. These findings remained significant after robust standard error correction. No other drug class demonstrated an independent association with REM latency.

3.5. NREM architecture

Anticonvulsant/antiepileptic use was associated with a redistribution of NREM sleep characterized by a reduction in light sleep (N1+N2) and an increase in slow-wave sleep (N3). No other classes were independently associated with NREM proportions.

3.6. Sleep continuity

Antipsychotic use was independently associated with a lower Arousal index, suggesting reduced sleep fragmentation. In contrast, antidepressant use was associated with a higher PLM index. No other class-specific associations were detected.

3.7. Independent effects of covariates and cumulative psychotropic burden

Results of covariate and cumulative burden analyses are presented in Table 5.

Age was independently associated with longer REM latency, lower sleep efficiency, increased WASO, and reduced mean nocturnal oxygen saturation. Higher BMI was associated with reduced N3 percentage and lower mean oxygen saturation. Male sex was associated with lower mean SpO_2 and lower Epworth Sleepiness Scale scores.

When cumulative psychotropic exposure was examined within the medicated group, a dose–response relationship emerged. Each additional psychotropic class was associated with a progressive increase in REM latency (Fig. 1) and a reduction in Arousal frequency, independent of age, sex, and BMI. No cumulative effects were observed for other architectural parameters.

Table 3
Distribution of psychotropic burden (n = 61).

Number of psychotropic classes	n	%
1 class	18	29.5%
2 classes	21	34.4%
3 classes	22	36.1%

Table 4
Adjusted associations between psychotropic drug classes and sleep outcomes
General linear models with Type III SS and HC3 robust SE. Adjusted for age, sex and BMI.
β represents adjusted mean difference (Yes vs No).
REM rapid eye movement sleep, *NREM* non rapid eye movement sleep, *N1+N2* non rapid eye movement light sleep, *N3* non rapid eye movement slow wave sleep, *PLM* periodic leg movement.

Domain	Outcome	Drug Class	β (95% CI)	p
REM regulation	REM latency (min)	Antidepressants	+64.34 (26.12 to 102.57)	0.001
	Sleep cycles (n)	Antidepressants	−1.22 (−1.77 to −0.67)	<0.001
NREM architecture	N1+N2 (%)	Anticonvulsant/ antiepileptic	−6.30 (−12.60 to −0.01)	0.050
	N3 (%)	Anticonvulsant/ antiepileptic	+5.50 (1.16 to 9.84)	0.013
Sleep continuity	Arousal index (n/h)	Antipsychotics	−3.63 (−6.10 to −1.16)	0.004
	PLM index (n/h)	Antidepressants	+6.54 (1.29 to 11.79)	0.015

Table 5
Independent associations of covariates and cumulative psychotropic burden
General linear models with Type III SS and HC3 robust SE. Adjusted for age, sex and BMI.
β represents adjusted mean difference (Yes vs No).

Outcome	Predictor	β (95% CI)	p
REM latency (min)	Number of classes (per +1)	+35.46 (3.67 to 67.24)	0.029
	Age (per year)	+2.77 (0.39 to 5.15)	0.023
Arousal index (n/h)	Number of classes (per +1)	−3.12 (−4.83 to −1.40)	0.001
Sleep efficiency (%)	Age (per year)	−0.206 (−0.389 to −0.023)	0.027
WASO (min)	Age (per year)	+0.928 (0.168 to 1.687)	0.017
N3 (%)	BMI (per kg/m^2)	−0.198 (−0.372 to −0.024)	0.026
Mean SpO_2 (%)	Age (per year)	−0.025 (−0.046 to −0.003)	0.025
	BMI (per kg/m^2)	−0.080 (−0.153 to −0.007)	0.031
	Male vs Female	−1.021 (−1.717 to −0.325)	0.004
ESS	Male vs Female	−3.352 (−5.752 to −0.952)	0.007

BMI body mass index, *ESS* Epworth sleepiness scale, *N3* non rapid eye movement slow wave sleep, *REM* rapid eye movement sleep, *WASO* wake after sleep onset, *SpO2* peripheral arterial oxygen saturation.

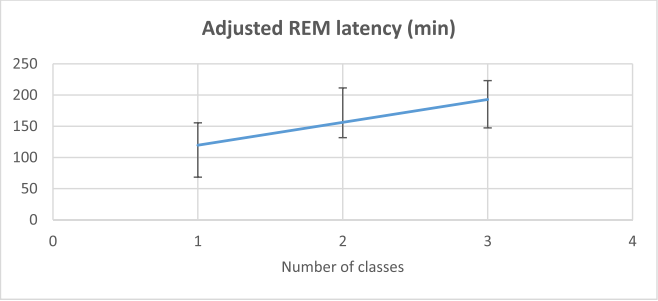

Fig. 1. Adjusted REM latency according to cumulative psychotropic exposure
REM rapid eye movement sleep.

4. Discussion

The present study examined the associations between psychotropic medication use and objective sleep architecture parameters in a clinically heterogeneous sample. By combining unadjusted comparisons with multivariable general linear models controlling for age, sex, and BMI, we sought to disentangle class-specific and cumulative pharmacological effects on REM sleep regulation, NREM sleep architecture, and sleep continuity. The findings suggest distinct and biologically coherent patterns: antidepressants were strongly associated with REM suppression and periodic limb movements (PLM), anticonvulsant/antiepileptic agents were associated with increased slow-wave sleep (N3), and antipsychotics were linked to reduced arousal frequency. Moreover, cumulative psychotropic burden exhibited a dose–response relationship with REM latency and arousal index. These findings contribute to an expanding body of literature on pharmacological modulation of sleep micro- and macrostructure.

The most robust finding was the independent association between antidepressant use and prolonged REM latency, accompanied by a reduction in the number of sleep cycles. This pattern is consistent with the well-established REM-suppressive properties of monoaminergic antidepressants. Recent findings confirm that SSRIs, SNRIs, and tricyclic antidepressants consistently delay REM onset and reduce REM density (Wichniak et al., 2017). SSRIs such as fluoxetine and SNRIs such as venlafaxine increase serotonergic and noradrenergic tone within pontine REM-generating circuits, inhibiting cholinergic REM-on neurons. Contemporary neurophysiological models highlight the reciprocal interaction between monoaminergic REM-off neurons and sublaterodorsal tegmental REM-on populations, providing mechanistic support for antidepressant-induced REM delay (Scammell et al., 2017), (Peever and Fuller, 2017). This finding should also be read against the psychiatric profile of the sample, since depressive disorders predominated in the psychotropic cohort. Untreated major depression is itself linked to REM disinhibition, with a shorter rather than longer REM latency, the opposite of what we observed, suggesting the REM-suppressive action of antidepressants outweighed any disease-related shortening. Still, our retrospective design did not allow psychiatric diagnosis, illness duration, and medication exposure to be fully disentangled, so the prolonged REM latency more likely reflects the combined effect of treated depression than a purely pharmacological one (Steiger and Pawlowski, 2019).

Antidepressants represent a heterogeneous pharmacological group, and individual compounds may exert different effects on sleep architecture according to their receptor profile and mechanism of action. Although REM suppression and prolonged REM latency are commonly described effects of serotonergic and noradrenergic antidepressants, other agents may exhibit distinct patterns of REM modulation. For example, bupropion, mirtazapine, and trazodone have been associated with different effects on REM parameters compared with classical REM-suppressing antidepressants. Therefore, the present findings should be interpreted as reflecting the predominant association of antidepressant exposure within this cohort rather than a universal effect of all antidepressant medications. Since medication effects were analyzed at the class level, the present study cannot determine whether specific antidepressant subclasses or individual compounds were primarily responsible for the observed association (Schramm et al., 2014).

Interestingly, while REM latency was markedly prolonged, total REM percentage was not significantly altered after adjustment. This apparent dissociation may reflect chronic adaptation phenomena. Long-term antidepressant treatment can produce partial REM rebound or redistribution across later sleep cycles, attenuating net reductions in REM proportion despite delayed onset (Wichniak et al., 2017), (Steiger and Pawlowski, 2019).

The observed reduction in total sleep cycles likely represents a downstream consequence of REM delay, as prolonged first-cycle NREM compresses ultradian cycling. Given that normal sleep architecture typically comprises four to five cycles per night (Cajochen et al., 2024), the loss of approximately one cycle may carry implications for emotional memory consolidation and affective processing, both strongly linked to REM integrity (Rawson and Jackson, 2024).

Although PLM did not differ descriptively between groups, antidepressant use emerged as an independent predictor of a higher PLM index. This finding is consistent with recent pharmacovigilance data and polysomnographic studies indicating that serotonergic antidepressants may precipitate or exacerbate periodic limb movements and restless legs symptoms, potentially via serotonergic modulation of spinal dopaminergic pathways and consequent interference with motor inhibitory control during sleep (Marey et al., 2025).

Anticonvulsant/antiepileptic group use was associated with decreased light sleep (N1+N2) and increased N3 percentage, suggesting a redistribution toward deeper NREM stages. Contemporary evidence supports the capacity of γ-aminobutyric acid (GABA)-modulating agents to enhance slow-wave activity through increased cortical synchronization (Carvalho et al., 2022). Agents such as gabapentin and pregabalin have been shown in recent randomized trials to increase slow-wave sleep and improve sleep maintenance in both neuropathic pain and epilepsy populations (Roliz and Kothare, 2022). The enhancement of N3 is physiologically relevant, as slow-wave sleep supports synaptic homeostasis, glymphatic clearance, and declarative memory consolidation (Tononi and Cirelli, 2020).

Antipsychotic use was independently associated with a lower arousal index, indicating reduced sleep fragmentation. This aligns with accumulating evidence that many second-generation antipsychotics exert sedative effects via histamine H1 and serotonin 5-HT2A receptor antagonism. For instance, quetiapine has demonstrated increased total sleep time and reduced nocturnal awakenings in polysomnographic studies of mood and psychotic disorders (Monti et al., 2017).

Regarding sleep fragmentation, the reduced arousals finding may translate into improved subjective sleep continuity; however, it is theoretically conceivable that excessive suppression of physiological arousability could theoretically attenuate protective respiratory responses. The modest reduction in mean nocturnal oxygen saturation observed in the psychotropic group at the descriptive level did not survive multivariable adjustment; age, BMI, and male sex emerged as the only independent predictors of SpO_2, indicating that the unadjusted difference was driven by demographic factors rather than by medication itself — a distinction with meaningful clinical implications when interpreting oxygen parameters in this population.

A key contribution of this study is the identification of a dose–response relationship between cumulative psychotropic exposure and specific sleep parameters. Each additional psychotropic class was associated with progressive REM latency prolongation and reduced arousal frequency.

Polypharmacy is increasingly prevalent in psychiatric practice, particularly in treatment-resistant mood and psychotic disorders (Pae, 2020). Neurochemically, concurrent modulation of serotonergic, noradrenergic, dopaminergic, GABAergic, and histaminergic systems may exert additive inhibitory effects on REM-generating circuits and ascending arousal pathways. The linear association observed here strengthens the biological plausibility of cumulative pharmacodynamic interaction.

Notably, cumulative burden did not significantly alter NREM distribution or sleep efficiency, indicating selective vulnerability of REM timing and arousal regulation to additive drug effects. Clinically, these findings underscore the importance of evaluating total psychotropic load when interpreting polysomnography, rather than attributing changes to single agents in isolation.

Consistent with contemporary normative data, age was independently associated with reduced sleep efficiency, increased wake after sleep onset (WASO), prolonged REM latency, and lower mean nocturnal oxygen saturation (Mander et al., 2017), (Simon et al., 2025). Age-related degeneration of sleep-regulatory circuits and reduced

homeostatic slow-wave pressure likely account for these findings. It is worth noting that WASO showed no significant between-group difference at the descriptive level and no independent association with any psychotropic class in the adjusted models; the age-related increase observed in Table 4 may reflect a normative pattern of sleep fragmentation with advancing age rather than a pharmacological effect.

Higher BMI was independently associated with reduced N3 percentage and lower oxygen saturation, reflecting the established link between adiposity, impaired slow-wave generation, and subclinical sleep-disordered breathing (Malhotra and White, 2002). Male sex predicted lower oxygen saturation and lower Epworth Sleepiness Scale scores, in line with sex differences in respiratory vulnerability and subjective sleep perception.

This study is limited by its observational design, precluding causal inference. Drug dosage, duration, timing of administration, and psychiatric illness severity were not incorporated into the models. Although psychiatric diagnoses and duration of illness were characterized descriptively within the psychotropic cohort, standardized measures of illness severity were not consistently available in the medical records due to the retrospective nature of the study and therefore could not be reliably included in the analyses. Consequently, residual confounding related to the underlying psychiatric disorders cannot be completely excluded. Additionally, microarchitectural measures such as spectral power or REM density were not assessed. No adaptation night was performed before polysomnography because recordings were obtained as part of routine clinical care using a single attended overnight Type I in-laboratory polysomnography. Consequently, a first-night effect may have influenced sleep onset latency, total sleep time, sleep efficiency, wake after sleep onset, and REM-related measures. Although both groups were studied under identical laboratory procedures, the magnitude of the first-night effect could not be quantified, and differential adaptation between groups cannot be excluded.

Controls were clinical referrals investigated for excessive daytime sleepiness rather than population-based volunteers. Nevertheless, the systematic exclusion of diagnosed sleep disorders, psychiatric conditions, and centrally acting medication yielded a comparator group with a level of clinical homogeneity that would be difficult to achieve in a community sample. Findings should therefore be interpreted within this specific clinical context. Future research should employ longitudinal designs with dose-stratified analyses, larger samples, and high-resolution EEG metrics to elucidate the mechanistic pathways underlying medication-related alterations in sleep architecture. In parallel, analyses at the level of individual compounds, incorporating treatment duration and pharmacodynamic profiles, are warranted to better characterize drug-specific effects on sleep architecture and disentangle the heterogeneity observed within pharmacological classes.

5. Conclusion

Psychotropic medications exert measurable, class-specific effects on sleep architecture. This is most evident through antidepressant-driven REM suppression, cyclicity reduction, and increased periodic limb movements; anticonvulsant-mediated enhancement of slow-wave sleep; and antipsychotic-associated reduction in arousal frequency. While these effects are often additive and predictable, their clinical significance varies depending on the therapeutic context and the psychotropic burden. Further studies incorporating dosage, serum monitoring, and broader interaction analyses are essential to clarify the long-term consequences of these alterations. Integrating polysomnography with cognitive and affective outcomes may ultimately determine whether these changes represent adaptive or maladaptive modifications of sleep physiology in medicated populations. Taken together, these results make a case for incorporating psychotropic burden into the routine clinical interpretation of polysomnography — a step that may improve the accuracy of sleep diagnoses and inform more targeted therapeutic decisions in psychiatrically medicated patients.

CRediT authorship contribution statement

Daniel Alfaiate: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Patrícia Silva:** Supervision, Methodology, Investigation, Data curation. **Patrícia Guerra:** Supervision, Investigation, Formal analysis. **Nuno Pinto:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Alexandre Pereira:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Authors' contributions

All authors approved the final version of the manuscript and agreed to its submission for publication.

Informed consent

Written informed consent for publication was obtained from all participants or their legal representatives. The privacy rights of the participants have been respected.

Ethical approval

This retrospective study was approved by the Ethics Committee of Centro Hospitalar do Médio Tejo (Approval No. 24/DC/CA). The study was conducted in accordance with applicable laws, regulations, institutional requirements, and the ethical principles of theDeclaration of Helsinki and its later amendments.

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Declaration of competing interest

The authors declare that they have no financial or non-financial competing interests or personal relationships that could have influenced the work reported in this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejphar.2026.179292.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of research participants and are subject to institutional and ethical restrictions.

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