

Association of as-needed (pro re nata) hypnotic administration frequency with hypnotic polypharmacy at discharge among hospitalized patients with depression: a retrospective observational study

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Abstract

Background

Insomnia is highly comorbid in patients with depression, and both hypnotic polypharmacy and as-needed (pro re nata, PRN) hypnotic use are common in clinical practice. Although repeated PRN use may reflect inadequate control of insomnia, its association with hypnotic polypharmacy at discharge remains unclear. This study therefore investigated the association between PRN hypnotic administration frequency during hospitalization and hypnotic polypharmacy at discharge in patients hospitalized for depression.

Methods

This single-center retrospective observational study included patients with depression admitted to the psychiatric ward of Toho University Omori Medical Center between January 2020 and June 2026. Patients were classified into polypharmacy (≥ 2 scheduled hypnotics at discharge) and non-polypharmacy (≤ 1 hypnotic) groups. The primary outcome was hypnotic polypharmacy at discharge, and the primary exposure was PRN hypnotic administration frequency during hospitalization (administrations/week). Multivariable logistic regression, sensitivity analysis, and receiver operating characteristic (ROC) analysis were performed to identify factors associated with hypnotic polypharmacy at discharge.

Results

A total of 103 patients were included, of whom 38 (36.9%) were discharged with hypnotic polypharmacy. PRN hypnotic administration frequency was significantly higher in the polypharmacy group than in the non-polypharmacy group (2.6 vs 0.6 administrations/week, $p < 0.001$). In multivariable analysis, PRN hypnotic administration frequency (adjusted odds ratio [aOR] per 1 administration/week increase, 2.59; 95% confidence interval [CI], 1.66–4.04) and hypnotic polypharmacy at admission (aOR, 9.70; 95% CI, 2.51–37.52) were independently associated with hypnotic polypharmacy at discharge. This association remained significant in a sensitivity analysis restricted to patients without hypnotic polypharmacy at admission. ROC analysis identified an optimal cutoff value of approximately 1.5 administrations/week (area under the curve, 0.833).

Conclusions

Among patients hospitalized for depression, more frequent PRN hypnotic administration during hospitalization was independently associated with hypnotic polypharmacy at discharge. PRN hypnotic administration frequency may serve as a clinically useful marker of persistent insomnia and treatment

refractoriness. Regular monitoring of PRN hypnotic administration, together with periodic multidisciplinary reassessment of scheduled hypnotic therapy, may facilitate appropriate hypnotic prescribing and help prevent unnecessary hypnotic polypharmacy. Further multicenter prospective studies are warranted to validate these findings.

Background

Insomnia commonly co-occurs with depression, affecting approximately 80–90% of patients and manifesting as difficulty initiating sleep, middle-of-the-night awakenings, or early-morning awakening [1, 2]. When insomnia persists, it may impede functional recovery, prolong depressive symptoms, and increase the risk of relapse. Its effective management should therefore be regarded as an integral component of depression treatment rather than solely as symptomatic care [1, 3, 4].

Hypnotics are consequently prescribed as adjunctive treatment for insomnia among patients with depression [1, 5, 6]. Although newer agents, including orexin receptor antagonists and melatonin receptor agonists, have broadened the available therapeutic options, hypnotic polypharmacy remains common in routine practice. Patients with persistent or clinically complex insomnia may receive multiple hypnotics with different mechanisms of action to address difficulties with sleep initiation and maintenance [3, 6]. However, hypnotic polypharmacy is associated with adverse outcomes, including excessive sedation, falls, cognitive impairment, and drug dependence [6, 7], without necessarily providing greater therapeutic benefit than appropriately selected monotherapy [6]. Optimizing hypnotic regimens and minimizing unnecessary polypharmacy are therefore important priorities in psychiatric pharmacotherapy.

Alongside scheduled hypnotic therapy, as-needed (*pro re nata*; PRN) hypnotics are commonly prescribed during hospitalization to address episodic or worsening insomnia [8]. Although PRN prescribing allows clinicians to respond flexibly to fluctuations in sleep symptoms, repeated administration may indicate that insomnia remains insufficiently controlled and may contribute to the continuation or intensification of hypnotic therapy [8]. Previous studies have examined psychotropic PRN prescribing practices and medication-monitoring programs [9]; however, the relationship between PRN hypnotic administration frequency and hypnotic polypharmacy remains insufficiently understood, particularly among patients hospitalized for depression.

Accordingly, this study examined the association between PRN hypnotic administration frequency during hospitalization and hypnotic polypharmacy at discharge among patients hospitalized for depression. Patterns of PRN hypnotic administration were also characterized to generate clinically relevant evidence that may support rational hypnotic prescribing and structured medication review.

Methods

Study design and patients

This study aimed to examine the association between PRN hypnotic administration frequency during hospitalization and hypnotic polypharmacy at discharge among patients hospitalized for depression and to characterize patterns of PRN hypnotic administration. This single-center retrospective observational study included patients with depression who were admitted to the psychiatric ward of Toho University Omori Medical Center from January 1, 2020, through June 30, 2026. Depression was diagnosed by the attending psychiatrist and documented in the electronic medical record; only patients with this documented diagnosis were eligible for inclusion. Each patient was observed from hospital admission to discharge. Patients were excluded if they received neither an antidepressant nor a hypnotic during hospitalization, had a hospital stay of ≤ 3 days, or were younger than 15 years. No a priori sample-size or power calculation was performed; all eligible patients admitted during the predefined study period were included.

Data collection and definitions

Demographic and clinical data were obtained from electronic medical records. The extracted variables included age, sex, body weight, height, comorbidities, length of hospital stay, admission type, use of seclusion or restraint, drinking history, smoking history, psychotropic prescriptions at admission and discharge, and PRN hypnotic administration during hospitalization. Individual PRN administrations were identified using medication administration records. Only confirmed diagnoses documented in the electronic medical records were classified as comorbidities.

Hypnotics were operationally defined as benzodiazepine receptor agonists (benzodiazepines and nonbenzodiazepines), orexin receptor antagonists (lemborexant and suvorexant), melatonin receptor agonists (ramelteon), and sedating antidepressants or antipsychotics (trazodone and quetiapine). In accordance with previous studies [10], trazodone and quetiapine were classified as hypnotics only when prescribed at bedtime at doses of ≤ 50 mg/day. The total number of hypnotics was calculated from scheduled prescriptions, with each pharmacologic agent counted once regardless of dose or formulation [11]. PRN hypnotics were excluded from the count of concomitant hypnotics.

For the present analysis, PRN hypnotic exposure was restricted to medications administered specifically for insomnia, including sleep-onset and sleep-maintenance insomnia; administrations for agitation were excluded. Because no standardized institutional criteria governed PRN administration, the choice of PRN hypnotic was determined by the attending physician.

Outcome measures

The primary outcome was hypnotic polypharmacy at discharge, defined as the prescription of two or more scheduled hypnotics. The primary exposure was PRN hypnotic administration frequency during hospitalization, measured as the number of administrations per week. This frequency was calculated by

dividing the total number of PRN hypnotic administrations by the duration of hospitalization and standardizing the resulting value to a weekly rate.

Patients were categorized at discharge according to the number of scheduled hypnotics prescribed: the polypharmacy group included patients receiving ≥ 2 hypnotics, whereas the non-polypharmacy group included those receiving ≤ 1 hypnotic. Hypnotic polypharmacy was defined in accordance with previous reports [6, 10].

Secondary outcomes comprised the types and timing of PRN hypnotic administrations. Consistent with institutional practice, the administration-time observation window was defined as 20:00, following the administration of scheduled bedtime medication, to 03:00, after which PRN hypnotics for insomnia were generally not administered.

Statistical analysis

Continuous variables were compared between groups using the Mann–Whitney *U* test, whereas categorical variables were compared using the chi-square test. Variables with a *p* value < 0.05 in the univariate analyses were considered for inclusion in the multivariable logistic regression model. Before model construction, multicollinearity was assessed using Pearson's correlation coefficient; when the absolute value of the correlation coefficient between two variables was ≥ 0.8 , one of the correlated variables was excluded. Multivariable logistic regression was subsequently performed using the forced-entry method. PRN hypnotic administration frequency was entered as a continuous variable, and the corresponding adjusted odds ratio is expressed per 1 administration/week increase. A sensitivity analysis was additionally performed in patients without hypnotic polypharmacy at admission ($n = 79$), using the same multivariable logistic regression procedure and the same covariates as in the primary analysis, except for hypnotic polypharmacy at admission, which was constant within this subgroup and was therefore excluded from the model.

Receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff value of PRN hypnotic administration frequency for identifying patients with hypnotic polypharmacy at discharge; the optimal cutoff was defined as the value that maximized the Youden index (sensitivity + specificity – 1). Continuous variables are presented as medians with interquartile ranges, and categorical variables as numbers and percentages. All tests were two-sided, and a *p* value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM® SPSS® Statistics, version 24 (IBM Japan, Tokyo, Japan).

Results

Patient characteristics

A total of 103 patients were included in the analysis (Table 1). The median age was 60.0 years (interquartile range, 39.5–75.0), 32 patients (31.1%) were male, and the median hospital stay was 36.0

days (interquartile range, 34.5–45.5). Of the study population, 56 patients (54.4%) were admitted involuntarily for medical care and protection, and 8 patients (7.8%) underwent seclusion or restraint during hospitalization.

Table 1
Baseline characteristics of the study population

No. of patients	103
Age (years)	60.0 (39.5–75.0)
Sex (male)	32 (31.1%)
Body weight (kg)	50.0 (43.2–58.4)
Height (cm)	158.1 (152.4–165.4)
Length of hospital stay (days)	36.0 (34.5–45.5)
Involuntary admission for medical care and protection	56 (54.4%)
Seclusion or restraint during hospitalization	8 (7.8%)
Number of hypnotic prescriptions at admission	
Benzodiazepines	
Nitrazepam	15 (14.6%)
Flunitrazepam	9 (8.7%)
Brotizolam	5 (4.9%)
Lormetazepam	1 (1.0%)
Triazolam	1 (1.0%)
Non-benzodiazepines	
Zolpidem	13 (12.6%)
Eszopiclone	4 (3.9%)
Others	
Lemborexant	25 (24.3%)
Trazodone	7 (6.8%)
Quetiapine	6 (5.8%)
Ramelteon	5 (4.9%)
Suvorexant	3 (2.9%)
Number of hypnotic prescriptions at discharge	
Benzodiazepines	
Data are presented as median (interquartile range) or n (%).	
Prescriptions were counted according to each active ingredient, irrespective of dose or formulation.	

No. of patients	103
Nitrazepam	13 (12.6%)
Brotizolam	8 (7.8%)
Flunitrazepam	7 (6.8%)
Non-benzodiazepines	
Eszopiclone	19 (18.4%)
Zolpidem	4 (3.9%)
Others	
Lemborexant	53 (51.5%)
Quetiapine	13 (12.6%)
Trazodone	9 (8.7%)
Ramelteon	5 (4.9%)
Suvorexant	2 (1.9%)
Data are presented as median (interquartile range) or n (%).	
Prescriptions were counted according to each active ingredient, irrespective of dose or formulation.	

[Insert Table 1 here]

At admission, lemborexant was the most frequently prescribed hypnotic (25 prescriptions), followed by nitrazepam (15) and zolpidem (13). Lemborexant remained the most frequently prescribed hypnotic at discharge (53 prescriptions), followed by eszopiclone (19) and nitrazepam (13). Mirtazapine and vortioxetine were the most commonly prescribed antidepressants at discharge.

Factors associated with hypnotic polypharmacy

At discharge, 38 patients (36.9%) were categorized into the polypharmacy group and 65 (63.1%) into the non-polypharmacy group (Table 2). Compared with the non-polypharmacy group, the polypharmacy group had a significantly higher median body weight (55.7 vs 48.3 kg, $p = 0.008$), greater PRN hypnotic administration frequency (2.6 vs 0.6 administrations/week, $p < 0.001$), a higher prevalence of hypnotic polypharmacy at admission (50.0% vs 7.7%, $p < 0.001$), and a greater proportion of patients with a smoking history (34.2% vs 15.4%, $p = 0.048$).

Table 2

Comparison of patient characteristics between the hypnotic polypharmacy and non-polypharmacy groups at discharge

Variable	Univariate analysis			Multivariable analysis	
	Polypharmacy (n = 38)	Non- polypharmacy (n = 65)	p value	aOR (95% CI)	p value
Age (years)	64.5 (42.2–75.8)	59.0 (35.0–75.0)	0.547 ^a		
Sex (male)	14 (36.8%)	18 (27.7%)	0.381 ^b		
Body weight (kg)	55.7 (46.7–64.0)	48.3 (41.7–57.2)	0.008 ^a	1.01 (0.98–1.05)	0.522
Height (cm)	161.2 (154.4–167.7)	155.8 (151.8–163.3)	0.136 ^a		
Involuntary admission for medical care and protection	18 (47.4%)	38 (58.5%)	0.310 ^b		
Seclusion or restraint during hospitalization	4 (10.5%)	4 (6.2%)	0.463 ^b		
Length of hospital stay (days)	36.0 (33.0–43.0)	37.0 (35.0–46.0)	0.808 ^a		
PRN hypnotic administration frequency (administrations/week)	2.6 (1.1–4.8)	0.6 (0.1–1.1)	< 0.001 ^a	2.59 (1.66–4.04)	< 0.001
Hypnotic polypharmacy at admission	19 (50.0%)	5 (7.7%)	< 0.001 ^b	9.70 (2.51–37.52)	0.001
Concomitant antipsychotics	8 (21.1%)	10 (15.4%)	0.592 ^b		
Concomitant anxiolytics	2 (5.3%)	5 (7.7%)	1.000 ^b		
Concomitant antiparkinsonian drugs	0 (0.0%)	0 (0.0%)	—		
Drinking history	10 (26.3%)	17 (26.2%)	1.000 ^b		
Data are presented as median (interquartile range) or n (%).					
^a Mann–Whitney <i>U</i> test; ^b chi-square test					
The aOR for PRN hypnotic administration frequency is expressed per 1 administration/week increase. aOR, adjusted odds ratio; CI, confidence interval; PRN, pro re nata.					

Variable	Univariate analysis			Multivariable analysis	
	Polypharmacy (n = 38)	Non- polypharmacy (n = 65)	p value	aOR (95% CI)	p value
Smoking history	13 (34.2%)	10 (15.4%)	0.048 ^b	2.62 (0.63– 10.83)	0.185
Comorbidities					
Hypertension	9 (23.7%)	16 (24.6%)	1.000 ^b		
Diabetes mellitus	5 (13.2%)	6 (9.2%)	0.529 ^b		
Hyperlipidemia/dyslipidemia	5 (13.2%)	8 (12.3%)	1.000 ^b		
Glaucoma	1 (2.6%)	5 (7.7%)	0.409 ^b		
Deep vein thrombosis	1 (2.6%)	4 (6.2%)	0.649 ^b		
Intervertebral disc herniation	1 (2.6%)	4 (6.2%)	0.649 ^b		
Osteoporosis	1 (2.6%)	3 (4.6%)	1.000 ^b		
Gastric cancer	2 (5.3%)	2 (3.1%)	0.625 ^b		
Cholelithiasis and related biliary disorders	2 (5.3%)	2 (3.1%)	0.625 ^b		
Bronchial asthma	3 (7.9%)	1 (1.5%)	0.141 ^b		
Data are presented as median (interquartile range) or n (%).					
^a Mann–Whitney <i>U</i> test; ^b chi-square test					
The aOR for PRN hypnotic administration frequency is expressed per 1 administration/week increase. aOR, adjusted odds ratio; CI, confidence interval; PRN, pro re nata.					

[Insert Table 2 here]

Because no clinically relevant multicollinearity was detected among these variables, all four were included in the multivariable logistic regression model. PRN hypnotic administration frequency (adjusted odds ratio [aOR] per 1 administration/week increase, 2.59; 95% confidence interval [CI], 1.66–4.04; $p < 0.001$) and hypnotic polypharmacy at admission (aOR, 9.70; 95% CI, 2.51–37.52; $p = 0.001$) were independently associated with hypnotic polypharmacy at discharge, whereas body weight and smoking history were not. In the sensitivity analysis restricted to patients without hypnotic polypharmacy at

admission (n = 79), PRN hypnotic administration frequency remained significantly associated with hypnotic polypharmacy at discharge (aOR, 2.57; 95% CI, 1.58–4.17; $p < 0.001$).

PRN hypnotic administration frequency increased with the number of hypnotics prescribed at discharge (Fig. 1). ROC analysis identified an optimal cutoff of approximately 1.5 administrations/week for distinguishing patients with hypnotic polypharmacy at discharge (area under the curve [AUC], 0.833; 95% CI, 0.748–0.918), with a sensitivity of 0.737 and a specificity of 0.877 (Fig. 2).

Patterns of PRN hypnotic administration during hospitalization

During hospitalization, the median PRN hypnotic administration frequency was 1.0 administrations/week (interquartile range, 0.4–2.4), and the median cumulative number of administrations was 5.0 per patient (interquartile range, 2.0–12.0).

Overall, 946 PRN hypnotic administrations were recorded, including 655 in the polypharmacy group and 291 in the non-polypharmacy group (Table 3). Lemborexant accounted for 87.3% of all PRN hypnotic administrations in the non-polypharmacy group. By contrast, administrations in the polypharmacy group were distributed across a broader range of hypnotics: lemborexant accounted for 41.8%, followed by eszopiclone (24.1%), trazodone (14.5%), brotizolam (5.6%), and quetiapine (5.0%). PRN hypnotic administration most frequently occurred at 22:00 in both groups. Administrations at 02:00 represented a slightly larger proportion in the polypharmacy group than in the non-polypharmacy group (14.5% vs 12.0%).

Table 3
Types and timing of PRN hypnotic administration during hospitalization

Variable	Polypharmacy at discharge (n = 38)	Non-polypharmacy at discharge (n = 65)	Total (n = 103)
Number of PRN administrations by hypnotic type			
Lemborexant	274 (41.8%)	254 (87.3%)	528 (55.8%)
Eszopiclone	158 (24.1%)	22 (7.6%)	180 (19.0%)
Trazodone	95 (14.5%)	3 (1.0%)	98 (10.4%)
Brotizolam	37 (5.6%)	0 (0.0%)	37 (3.9%)
Quetiapine	33 (5.0%)	3 (1.0%)	36 (3.8%)
Ramelteon	23 (3.5%)	6 (2.1%)	29 (3.1%)
Zolpidem	20 (3.1%)	0 (0.0%)	20 (2.1%)
Nitrazepam	11 (1.7%)	0 (0.0%)	11 (1.2%)
Flunitrazepam	4 (0.6%)	0 (0.0%)	4 (0.4%)
Suvorexant	0 (0.0%)	3 (1.0%)	3 (0.3%)
Number of PRN administrations by time of administration			
20:00	14 (2.1%)	4 (1.4%)	18 (1.9%)
21:00	31 (4.7%)	10 (3.4%)	41 (4.3%)
22:00	229 (35.0%)	107 (36.8%)	336 (35.5%)
23:00	124 (18.9%)	61 (21.0%)	185 (19.6%)
00:00	88 (13.4%)	40 (13.7%)	128 (13.5%)
01:00	74 (11.3%)	34 (11.7%)	108 (11.4%)
Total number of administrations: polypharmacy group, 655; non-polypharmacy group, 291; overall, 946. Data are presented as the number of administrations (%).			
PRN, pro re nata.			

Variable	Polypharmacy at discharge (n = 38)	Non-polypharmacy at discharge (n = 65)	Total (n = 103)
Number of PRN administrations by hypnotic type			
02:00	95 (14.5%)	35 (12.0%)	130 (13.7%)
Total number of administrations: polypharmacy group, 655; non-polypharmacy group, 291; overall, 946. Data are presented as the number of administrations (%).			
PRN, pro re nata.			

[Insert Table 3 here]

Discussion

In this retrospective study of patients hospitalized during the acute phase of depression, more frequent PRN hypnotic administration during hospitalization and hypnotic polypharmacy at admission were independently associated with hypnotic polypharmacy at discharge. Previous studies have described psychotropic PRN prescribing patterns at discharge [12], examined associations between PRN medication use and clinical outcomes [13, 14], and assessed PRN prescription-monitoring programs [8]. However, the clinical implications of the frequency of actual PRN hypnotic administrations have remained insufficiently understood. To our knowledge, this is the first study to quantify PRN hypnotic administration frequency directly from medication administration records and demonstrate its independent association with hypnotic polypharmacy at discharge. Because this measure can be readily derived from routinely collected prescribing and administration data, it may provide an objective, practical, and reproducible indicator for identifying patients at greater risk of hypnotic polypharmacy. The association also persisted in the sensitivity analysis restricted to patients without polypharmacy at admission, supporting PRN hypnotic administration frequency as an independent indicator rather than merely a correlate of the preadmission prescribing regimen.

PRN hypnotics are prescribed to manage episodic or worsening insomnia; however, repeated administration may indicate insufficient symptom control despite scheduled therapy. Reliance on PRN medication may also postpone timely reassessment of the maintenance regimen when its short-term effectiveness is interpreted as adequate overall control of insomnia [8]. In acute psychiatric wards, where patients are often admitted during periods of severe illness, some PRN hypnotic administration may be clinically necessary. Nevertheless, the present findings suggest that PRN hypnotic administration frequency should be interpreted not only as a reflection of symptom burden but also as a potentially actionable clinical signal.

ROC analysis identified approximately 1.5 administrations per week as the optimal cutoff for distinguishing patients with and without hypnotic polypharmacy at discharge, with good discriminatory performance. Although this threshold requires external validation, it may offer clinicians a practical point at which to initiate a structured medication review before frequent PRN administration becomes an established treatment pattern. Repeated PRN administration should prompt reassessment of insomnia symptoms, evaluation of the scheduled hypnotic regimen, and consideration of nonpharmacologic interventions rather than the routine continuation of PRN prescriptions.

Within this process, pharmacists may contribute by systematically reviewing PRN administration records and collaborating with psychiatrists and nursing staff to promote rational hypnotic prescribing. Thus, PRN hypnotic administration frequency may reflect more than episodic symptom management; it may also serve as an indirect indicator of persistent or treatment-refractory insomnia.

Hypnotic polypharmacy at admission showed the strongest association with hypnotic polypharmacy at discharge, indicating that medication regimens established before hospitalization may remain difficult to modify during a single acute-phase admission. This finding is clinically plausible because insomnia associated with depression may persist even as depressive symptoms improve. Sleep-maintenance insomnia and early-morning awakening, in particular, may respond less favorably to hypnotic therapy than sleep-onset insomnia [1, 3]. Residual insomnia is also among the most common symptoms persisting after remission and is associated with an increased risk of depressive relapse [15, 16]. In this context, repeated PRN administration may contribute to the intensification of scheduled hypnotic therapy as clinicians attempt to manage unresolved sleep symptoms, potentially leading to hypnotic polypharmacy at discharge. Once a multidrug hypnotic regimen has been established, dose reduction or discontinuation may be challenging [7, 17]. In addition, long-term hypnotic prescribing has been associated with broader psychotropic polypharmacy in routine clinical practice [18]. Collectively, hypnotic polypharmacy at admission and frequent PRN hypnotic administration may represent complementary indicators of persistent or treatment-refractory insomnia rather than entirely separate prescribing patterns. These findings underscore the importance of reassessing hypnotic therapy early during hospitalization, particularly among patients admitted with preexisting hypnotic polypharmacy.

Patterns of PRN hypnotic administration provide additional insight into the clinical context of hypnotic polypharmacy at discharge. In the non-polypharmacy group, lemborexant accounted for most PRN administrations, whereas administrations in the polypharmacy group involved a broader range of hypnotics, including eszopiclone, trazodone, brotizolam, and quetiapine. Orexin receptor antagonists and melatonin receptor agonists are generally considered to carry lower risks of dependence and rebound insomnia than benzodiazepine receptor agonists, while eszopiclone has demonstrated sustained efficacy during long-term treatment [19, 20]. Trazodone and quetiapine have also been associated with hypnotic polypharmacy in routine clinical practice [18]. The broader distribution of PRN hypnotics in the polypharmacy group should not be interpreted as evidence of the superiority of any specific agent. Instead, it may reflect repeated attempts to manage persistent or treatment-refractory insomnia through different pharmacologic approaches following an insufficient response to the existing regimen. The

overall distribution of PRN administration times was similar between the groups, with the highest frequency observed at approximately 22:00. However, administrations at 02:00 represented a slightly larger proportion in the polypharmacy group, potentially aligning with previous evidence that later-night sleep disturbances are associated with more complex hypnotic regimens [6]. Because these findings are descriptive, they should be interpreted cautiously. Nevertheless, the observed pattern may indicate that patients discharged with hypnotic polypharmacy experienced more persistent nighttime insomnia requiring repeated pharmacologic management. The pronounced administration peak at 22:00 may also reflect institutional practices, including the timing of scheduled bedtime medication and the defined window for PRN hypnotic administration.

This study has some limitations. First, its retrospective, single-center design may limit the generalizability of the findings. Institution-specific prescribing practices, nurse-mediated PRN administration, and local operational procedures may have influenced the observed associations. Second, the clinical circumstances surrounding individual PRN administrations could not be fully assessed, including the prescribing physician's rationale, nursing evaluation, patient preference, and perceived medication response. Third, although the multivariable analysis accounted for measured covariates, residual confounding may remain because clinically relevant factors, including depression severity, insomnia severity, hypnotic exposure before admission, and nonpharmacologic insomnia management, were unavailable or incompletely captured. Fourth, analyses of PRN hypnotic type and administration timing were descriptive and based on the total number of administrations; therefore, they may have been influenced by a relatively small number of frequent users. Finally, because of the observational design, causal relationships between PRN hypnotic administration frequency and hypnotic polypharmacy at discharge cannot be established.

Despite these limitations, the findings suggest that systematic monitoring of PRN hypnotic administration frequency, combined with periodic multidisciplinary reassessment of scheduled hypnotic regimens, may support rational prescribing and reduce unnecessary hypnotic polypharmacy at discharge. Future multicenter prospective studies should externally validate the proposed cutoff, examine the clinical mechanisms underlying the association between frequent PRN administration and discharge polypharmacy, and determine whether monitoring-based interventions can reduce unnecessary hypnotic polypharmacy and improve patient outcomes.

Conclusions

Among patients hospitalized for depression, more frequent PRN hypnotic administration during hospitalization and hypnotic polypharmacy at admission were independently associated with hypnotic polypharmacy at discharge. PRN hypnotic administration frequency may provide an objective measure of medication exposure and a clinically useful indicator of persistent or treatment-refractory insomnia. Systematic monitoring of PRN administrations, combined with periodic multidisciplinary reassessment of scheduled hypnotic regimens, may support rational prescribing and reduce unnecessary hypnotic polypharmacy at discharge. Further prospective, multicenter studies are needed to externally validate

these findings and determine whether interventions guided by PRN hypnotic administration frequency can reduce polypharmacy while improving patient outcomes.

Abbreviations

aOR
adjusted odds ratio
AUC
area under the curve
CI
confidence interval
PRN
pro re nata (as-needed)
ROC
receiver operating characteristic.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and the "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" and was approved by the Ethics Committee of Toho University Omori Medical Center (approval number: T2026-089). Because this was a retrospective observational study, the requirement for individual informed consent was waived by the ethics committee, and research information was disclosed by an opt-out procedure, thereby guaranteeing the opportunity to refuse participation.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KS designed the study, collected and analyzed the data, and drafted the manuscript. YH contributed to the study design, data interpretation, and manuscript revision. HT, TY, H. Ohashi, H. Otani, KA, TN, and TM contributed to data collection and to the clinical interpretation of the findings, and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

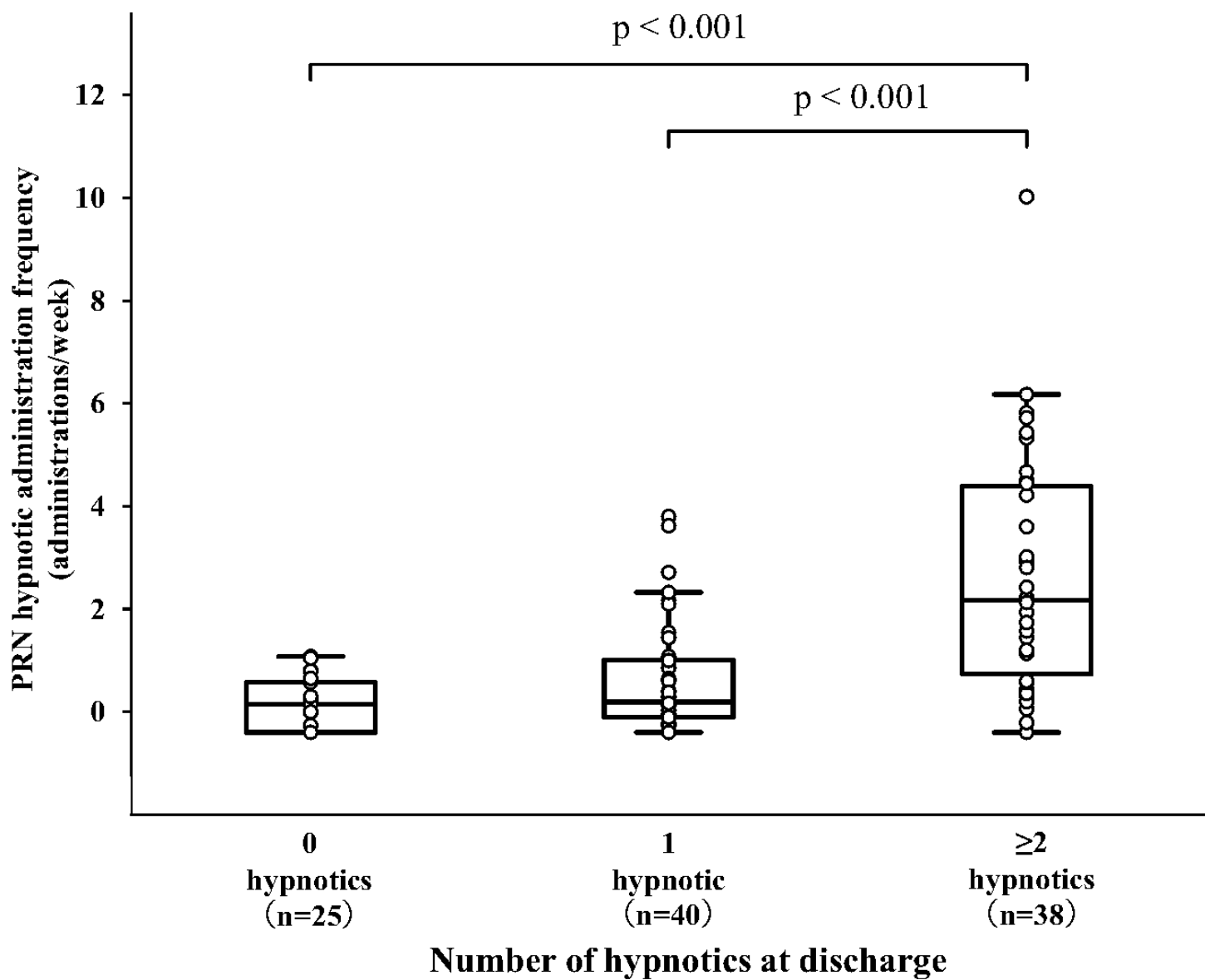


Figure 1

PRN hypnotic administration frequency according to the number of hypnotics prescribed at discharge.

Box plots indicate the median and interquartile range; whiskers extend to the most extreme values within 1.5 times the interquartile range, and circles represent individual patients. Horizontal brackets indicate pairwise comparisons, with p values calculated using the Mann–Whitney U test. PRN, pro re nata.

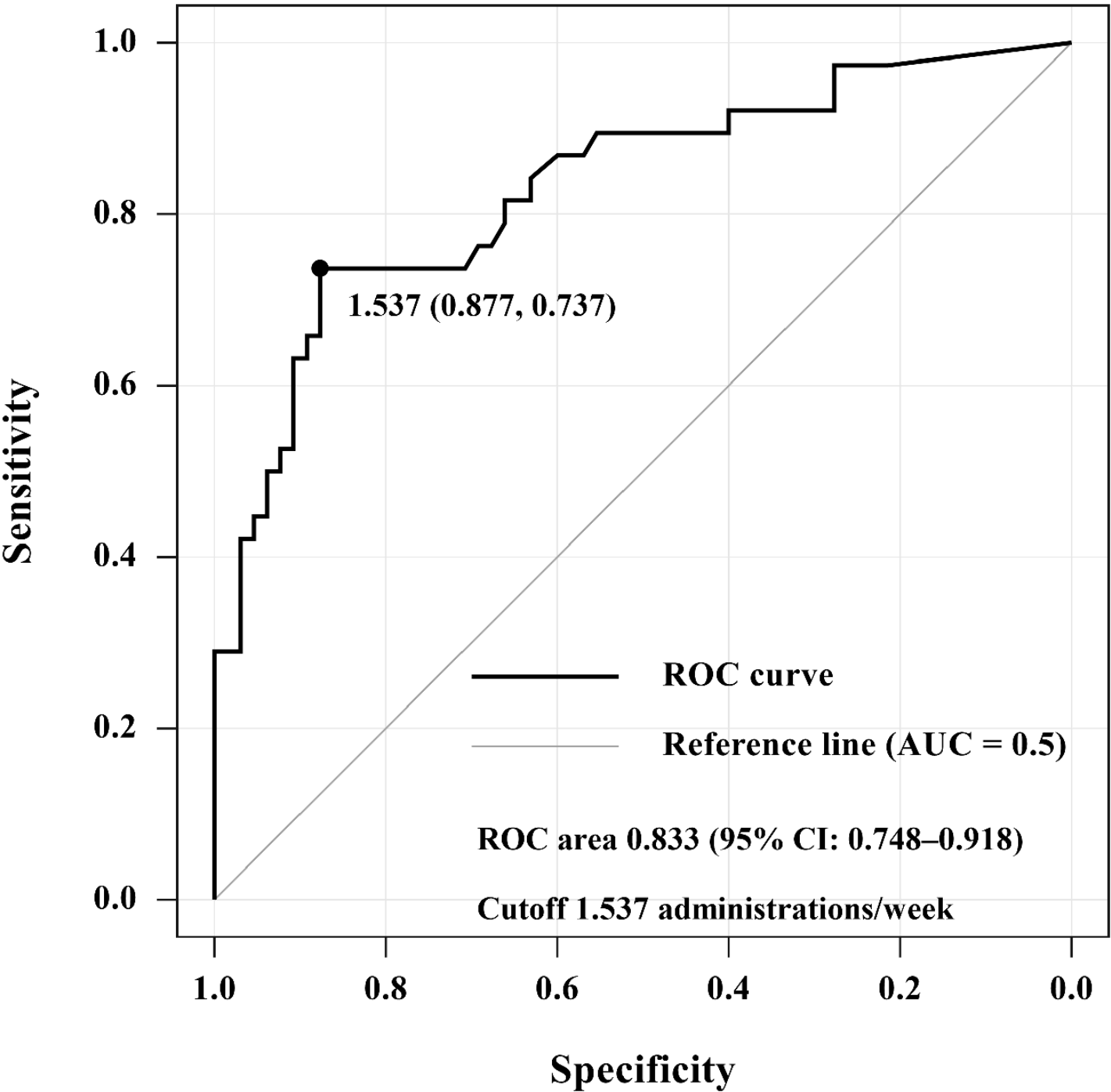


Figure 2

Receiver operating characteristic curve of PRN hypnotic administration frequency for predicting hypnotic polypharmacy at discharge.

The solid line represents the receiver operating characteristic (ROC) curve, and the gray diagonal line indicates the reference line (AUC = 0.5). AUC, area under the curve; PRN, pro re nata.