

Hypnotic medication use among inpatients with schizophrenia and major depressive disorder: results of a nationwide study

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The institution at which the work was performed: Analysis was performed at Kyoto University. Clinical trial name, URL, and registration number: Effectiveness of Guideline for Dissemination and Education in Psychiatric Treatment, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000026044, R000026044

Total word count: 2,918

Total number of Tables: 5

Total number of Figures: 1

Total number of Supplementary Tables: 1

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Abstract:

Study objectives: To investigate the proportion of inpatients with schizophrenia and major depressive disorder prescribed hypnotic medication, and the association between such medication and the use of other antipsychotic agents.

Methods: This was a nationwide cross-sectional study performed as part of the 'Effectiveness of Guidelines for Dissemination and Education in Psychiatric Treatment' (EGUIDE) project. Data from 2146 inpatients with schizophrenia and 1031 inpatients with major depressive disorder were analyzed. All types and dosages of psychotropic drugs were recorded and the data at the time of discharge were analyzed. Associations between the use of hypnotic medication and other antipsychotic agents were evaluated using multivariate logistic regression analyses.

Results: The proportions of schizophrenia patients who were prescribed any and two or more hypnotic agents were 55.7% and 17.6%, respectively, and the corresponding proportions for patients with major depressive disorder were 63.6% and 22.6%, respectively. In schizophrenia patients, multivariate logistic regression analyses showed that two or more antipsychotics, anticholinergic drugs, anxiolytics, and mood stabilizers/antiepileptic drugs were positively associated with the use of any hypnotic agent. In patients with major depressive disorder, multivariate logistic regression analyses revealed that two or more antidepressants, two or more antipsychotics, anxiolytics, and mood stabilizers/antiepileptic drugs were positively associated with the use of any hypnotic agent.

Conclusions: Prescription of hypnotic agents was found to be highly frequent among inpatients with psychiatric disorders. Prescription of two or more main antipsychotic agents was commonly associated with the use of hypnotic medication for both schizophrenia and major depressive disorder.

Keywords: hypnotic medication; schizophrenia; major depressive disorder; insomnia; antipsychotic; antidepressant

ABBREVIATIONS

SZ, schizophrenia

MDD, major depressive disorder

BZD, benzodiazepine

EGUIDE, Effectiveness of Guidelines for Dissemination and Education in Psychiatric Treatment

mECT, modified electroconvulsive therapy

ATC, Anatomical Therapeutic Chemical

OR, odds ratio

CI, confidence intervals

BPRS, Brief Psychiatric Rating Scale

HAM-D, Hamilton Rating Scale for Depression

ISI, Insomnia Severity Index

1. Introduction

Insomnia is a common problem for patients with psychiatric disorders, and previous studies have reported that it affects up to 80% of patients with schizophrenia[1] and up to 90% of patients with depression.[2] Biological studies have reiterated the important etiological link between these two conditions.[3, 4] Clinical studies of patients with psychiatric disorders have shown that such insomnia is associated with cognitive decline, depressive symptoms, metabolic syndrome, a low quality of life, and suicide risk,[5-8] thus representing a clinically important issue.

Evidence for the efficacy of hypnotic medication during the treatment of schizophrenia (SZ) and major depressive disorder (MDD) is limited. For SZ, some clinical trials have found that co-administration of hypnotics in addition to antipsychotic treatments leads to significantly greater improvement of insomnia[9] and a reduction of psychiatric severity.[10] For patients with MDD, several clinical studies have shown that co-administration of hypnotics in addition to antidepressants leads to significantly greater improvement of insomnia and depressive symptoms in patients suffering from both.[11, 12] However, data on the long-term symptom outcome for psychiatric patients are relatively sparse. Numerous studies have documented various side effects of hypnotic medications (e.g., benzodiazepines (BZDs)), including falls, delirium, acute respiratory failure, dependence, and withdrawal symptoms,[13-15] as well as an increased risk of suicide, among psychiatric patients.[16] The risks of such side effects are increased when hypnotics are used in high doses and/or over the long term.[17] In such a situation, although short-term use of sedative/hypnotics may be effective for relief of distress, insomnia, and behavioral disturbances secondary to psychosis, clinical guidelines restricting long-term prescription of sedative/hypnotic agents have been developed for SZ and MDD patients in both Japan[18, 19] and western countries.[20, 21]

Few studies have addressed the prevalence of hypnotic medication use in the treatment of psychiatric disorders. Although some studies have investigated the prevalence of concomitant

benzodiazepine use,[22, 23] they did not accurately reflect the prevalence of hypnotic medication use because benzodiazepines are used for not only hypnotic medication but also as anxiolytics and anticonvulsants. In addition, many hypnotic and sedative medications other than benzodiazepines have been used in clinical settings. Some studies on the prevalence of sedative/hypnotics have reported that fewer than one third of SZ outpatients[24] and MDD patients[25] received sedatives/hypnotics. However, those data were derived from clinical trials of antipsychotics and antidepressants and did not necessarily reflect the actual clinical setting. The study of a large administrative insured claims database found that the percentage of BZD and hypnotics were used by 33.1% and 16.9% in patients with MDD, though there may have been errors in coding and recording, potentially resulting in a misrepresentation of a proportion of patients' diagnoses.[26] There may be an evidence-practice gap regarding hypnotic medication use in patients with psychiatric disorders, as such agents have been widely applied in actual clinical practice even though some clinical guidelines do not recommend their long-term use.[18-21]

The present study was conducted as part of the 'Effectiveness of Guidelines for Dissemination and Education in Psychiatric Treatment' (EGUIDE) project. The primary aim of this project is to assess the dissemination of the guidelines via educational programs for psychiatrists throughout Japan and to evaluate the educational effectiveness of those programs for individual psychiatrists.[27] Although few studies have investigated the use of hypnotic medication among SZ and MDD inpatients in a clinical setting, we were interested in whether an evidence-practice gap might exist between clinical guidelines and clinical practice for such inpatients. It was anticipated that if the actual prevalence of hypnotic medication use could be clarified, and the factors associated with the use of these agents identified, such an evidence-practice gap might become apparent, thus being educationally effective for physicians and leading to an improvement in patient QOL.

In the present study, we analyzed hypnotic medication use and associated factors in

inpatients with SZ and MDD using data from a large cross-sectional, nationwide survey. The study aims were: (1) to examine the proportion of such patients receiving hypnotic medication; and (2) to investigate the association between the prescription of hypnotic medication and that of other antipsychotic agents in those patients. We were specifically interested in whether other psychotropic medications were commonly used together with hypnotic medication in SZ patients and MDD patients.

2. Methods and Materials

2.1. Study participants and data collection

This study was performed as part of the 'Effectiveness of Guidelines for Dissemination and Education in Psychiatric Treatment' (EGUIDE) project, as we have reported previously in detail.[27-34] This was an ongoing cross-sectional, nationwide survey conducted from 2016. The project's primary aim was to assess the dissemination of the guidelines via educational programs for psychiatrists throughout Japan and to evaluate the educational effectiveness of those programs for individual psychiatrists. A total of 83 institutions (37 university hospitals, 23 national/public/private general hospitals, and 33 national/public/private psychiatric hospitals) participated in the project. The diagnoses of SZ and MDD were confirmed by the treating psychiatrists of each study site. In the EGUIDE project prescription survey, we recorded all types and dosages of psychotropic drugs at the time of both admission and discharge. All psychotropic drugs were classified into antipsychotics, antidepressants, anticholinergic drugs, anxiolytics, mood stabilizers/antiepileptic drugs, hypnotic medications, and not classifiable. We calculated the psychotropic dose equivalence.[35] Information on treatment using modified electroconvulsive therapy (mECT) and the number of rehospitalizations for those patients was also collected. The EGUIDE project members were responsible for data collection at each study site using a standardized data collection method that checked their medical records and manually entered them into an Excel sheet.

This study was approved by the ethics committees of the National Center of Neurology and Psychiatry and the various participating hospitals.

Data on prescriptions for patients with SZ and MDD at the time of discharge (April to September, 2016-2018) were selected for the present analysis. The total number of patients was 2376 for SZ and 1142 for MDD. Data for rehospitalization during the study period (n=110 for SZ and n=43 for MDD) were excluded. After 10 psychiatric experts had checked all the prescription data (n=6 for SZ, n=7 for MDD), participants for whom prescription information was incomplete, considered to have been mistyped, or for whom extremely high doses were recorded (n=120 for SZ, n=68 for MDD) were omitted. Finally, we analyzed data from a final sample of 2146 for the SZ data set, and 1031 for the MDD data set. (**Fig. 1**)

2.2. Procedures

2.2.1. Measures of prescription

A list of codes for the generic names of medications considered to be hypnotics according to the Anatomical Therapeutic Chemical (ATC) Classification System[36] in N05C is shown in **Supplementary Table 1**. Eighteen of the medications were defined as hypnotics in the present study. We counted the number of hypnotic medication types used per day. The use of hypnotic medication was categorized as “any” or “two or more” according to the number of types used per day. The uses of antipsychotics and antidepressants were also categorized in a similar manner.

Any anticholinergic drugs, anxiolytics, and mood stabilizers/antiepileptic drugs were defined as having been administered as one or more per day.

2.2.2. Other measures

This study assessed sociodemographic information (age, sex), study site (university hospitals, national/public/private general hospitals, and national/public/private psychiatric

hospitals), and treatment using mECT. Age was divided into five groups: 0 to 19 years, 20 to 39 years, 40 to 59 years, 60 years to 79 years, and 80 years of age and older. Study sites were divided into two types: university hospitals and other hospitals.

2.3. Statistical analyses

Sex, age, and group differences in the percentage of hypnotic medication use in the SZ dataset and MDD dataset were examined using χ^2 test to investigate differences in categorical variables.

After crude logistic regression analyses, we conducted multivariate logistic regression analyses to examine the factors associated with “use of any hypnotic medication” and “use of two or more hypnotic medications” for both the SZ data set and the MDD dataset.

Explanatory variables in the present study were sex, age, study site, mECT, antipsychotics, antidepressants, anticholinergic drugs, anxiolytics, and mood stabilizers/antiepileptic drugs. Also, three categories of antipsychotic use – “two or more” “one” and “no” – were selected as explanatory variables for analyses of the SZ data set, and the same three categories of antidepressant use were selected as explanatory variables for analyses of the MDD data set.

All analyses were performed using SPSS 27.0 for Windows. Results were expressed as odds ratios (OR) and 95% confidence intervals (CI).

3. Results

Table 1 shows the relative proportions of the numbers of hypnotic medications used according to sex and age group. The mean number of hypnotic medications used in the SZ and MDD groups was 0.76 ± 0.79 ($m \pm SD$) and 0.90 ± 0.80 , respectively. In the SZ data set, the relative proportions of use of any hypnotic medication and two or more hypnotic medications were 56.4% and 17.8%, respectively. In the MDD data set, the relative proportions of use of any

hypnotic medication and two or more hypnotic medications were 64.9% and 23.1%, respectively. Significant ($\chi^2 = 36.15$, $df = 8$, $P < 0.001$ for SZ, $\chi^2 = 36.69$, $df = 8$, $P < 0.001$ for MDD) age-group differences in both the SZ data set and MDD data set were observed. The proportion of patients receiving hypnotic medication increased in middle age (40-59y) and decreased in both younger and older age in both the SZ and MDD data sets. The percentage of each hypnotic medication prescribed is shown in **Supplementary Table 1**.

The association between hypnotic medication and administration of other antipsychotics in SZ patients is shown in **Table 2, 3**. Multivariate logistic regression analyses revealed that the use of two or more antipsychotics, anticholinergic drugs, anxiolytics, and mood stabilizers/antiepileptic drugs was positively associated with the use of any hypnotic medication (**Table 2**). Multivariate logistic regression analyses also revealed that the use of two or more antipsychotics and mood stabilizers/antiepileptic drugs was positively associated with the use of two or more hypnotic medications (**Table 3**). Dosage of chlorpromazine equivalents by the number of antipsychotics (zero, one, two or more) in the SZ dataset was 2.3 ± 15.1 , 469.4 ± 262.7 , and 958.0 ± 489.4 , respectively.

The association between hypnotic medications and the use of other antipsychotics in MDD patients is shown in **Table 4, 5**. Multivariate logistic regression analyses revealed that the use of two or more antidepressants, anxiolytics, and mood stabilizers/antiepileptic drugs was positively associated with the use of any hypnotic medication (**Table 4**). Multivariate logistic regression analyses also revealed that the use of two or more antidepressants, antipsychotics, and anxiolytics was positively associated with the use of two or more hypnotic medications (**Table 5**). Dosage of imipramine equivalents by number of antidepressants (zero, one, two or more) in the MDD dataset was 0.0 ± 0.0 , 136.6 ± 70.7 , and 280.2 ± 134.1 , respectively.

4. Discussion

This is the first study to have evaluated the proportion of inpatients with SZ and MDD

receiving hypnotic medication and the association between hypnotic medication use and prescription of other antipsychotics based on data from a large cross-sectional nationwide survey in Japan. We found that more than half of the study participants were prescribed hypnotic medication, suggesting that there is an evidence-practice gap between clinical guidelines[18-21] and clinical practice. We also found that prescription of two or more main antipsychotic agents was commonly associated with hypnotic medication use for the treatment of SZ and MDD. These features have not been highlighted in previous surveys of psychotropic prescription conducted in Japan or other countries.

Several previous epidemiological studies of the general adult population in Japan found that the proportion of individuals receiving hypnotic medication was 3.1-3.6%.[37, 38] A clinical study of SZ outpatients found that 11.2% received sedative/hypnotics.[24] A meta-analysis of clinical trials involving patients with MDD found that 29.6% were prescribed sedative drugs.[25] Our present study revealed that more than half of the participants were prescribed hypnotic medication, representing a greater proportion than in previous studies.[24, 25] Such a difference may be partly attributable to differences in the survey setting, i.e. whether outpatients or inpatients were investigated. Previous studies found that hospitalization itself was associated with hypnotic medication use[39] and was considered to be a predictor of chronic insomnia.[40] Previous epidemiological studies found that age was a strong predictor of the prevalence of hypnotic medication use and that the use of such medication increased with age.[37, 38, 41] In the present study, the prevalence of hypnotic medication use increased in middle age (40-59y) and decreased in younger and older age in both SZ patients and MDD patients. This tendency was more evident in patients who were prescribed two or more hypnotic agents. These results suggest that the association between age and hypnotic medication use in psychiatric patients in the setting of hospitalization differs critically from that in the general adult population. Since younger and older adults may be at higher risk of side effects such as falls, delirium, acute respiratory failure, dependence, and withdrawal symptoms than other age

groups[14], physicians may be less likely to prescribe hypnotic medications.

The present study revealed that hypnotic medication was associated with the use of two or more main antipsychotic agents, i.e., antipsychotics for SZ, and antidepressants for MDD. These features were commonly found in both SZ patients and MDD patients. There are several possible interpretations of this association. One interpretation may be based on the severity of the disease. In patients with severe psychiatric conditions, symptoms of agitation, increased activity, or circadian rhythm disruption may be associated with an increase in the dose of the main psychotropic medication. Previous research found an association between severity of symptoms and antipsychotic polypharmacy.[42] Another interpretation may be based on the severity of insomnia, including reduced sleep time and poor sleep quality. In patients with severe insomnia, hypnotic agents and other antipsychotic medications with a sedative profile may be used additionally.[43] Off-label prescribing of antidepressants and antipsychotics is common, despite the lack of strong scientific evidence for their efficacy.[44] The third consideration is the conditions prevailing in individual hospitals, such as disruptive sleep environments, the staff with inadequate awareness of the harms associated with hypnotic medication use, and a shortage of private rooms, all of which may affect these associations.[39, 45]

In patients with SZ, the use of any hypnotic medication was significantly associated with that of anticholinergic drugs, anxiolytics, and mood stabilizers/antiepileptic drugs. In patients with MDD, the use of any hypnotic medication was significantly associated with that of anxiolytics, and mood stabilizers/antiepileptic drugs. The association between hypnotic medication use and other psychotropic agents may be influenced by both patient factors and prescriber factors.[46] Among patient-related factors, clinical symptoms and/or side effects of medication may influence the choice of psychotropic medications that are used concomitantly. Anticholinergic drugs may be prescribed to counter extrapyramidal motor side effects.[47] Some anxiolytics are used to treat not only anxiety symptoms but also insomnia, in view of their

sedative properties.[17] Adjunctive mood stabilizers for SZ may be prescribed for patients who have problems with impulse control and aggressive behavior, or for patients with schizoaffective disorder.[48, 49] In MDD patients, mood stabilizers/antiepileptic drugs are often used for augmentation therapy.[50] Because the participants of this survey were selected from among inpatients, our results may have been affected by the presence of severe and complex conditions. With regard to prescriber factors, it is possible that a physician's prescription pattern may be biased toward his or her own medical experience rather than clinical guidelines, or that the physician may opt for dose increases or augmentation therapy rather than switching when medication proves ineffective.[28, 29] Since our findings suggest that hypnotic medication use was significantly associated with prescription of other psychotropic medications, a prospective study is warranted to examine the complex interactions that can occur among hypnotic agents and other psychotropic medications in psychiatric patients. Furthermore, in future studies, it is necessary to examine in detail not only the prescriptions at discharge but also the changes in prescriptions during hospitalization.

There were several limitations to our study. First, causal relationships could not be determined since a cross-sectional design was adopted. Further prospective studies will be required to clarify the nature of the actual causal relationships between hypnotic medication use and related factors. Second, clinical data related to symptoms and disease severity were not assessed using rating scales. The use of clinical symptom measures (e.g., the Brief Psychiatric Rating Scale (BPRS), the Hamilton Rating Scale for Depression (HAM-D), or the Insomnia Severity Index (ISI)) will therefore be required in future studies. Third, there may have been a selection bias, because all participating sites were institutions that voluntarily cooperated with the study and were not selected randomly. Fourth, since there is a possibility that some study sites do not include all patients within the study period, the possibility of sampling bias should be noted. Fifth, many factors associated with hypnotic medication use, such as insomnia, anxiety, substance use, and days of hospitalization were not included in the present study. In the

future study, it would be important these variables could be included as correlates.

5. Conclusion

Using data from a large cross-sectional, nationwide survey in Japan, the present study has clarified the prevalence of hypnotic medication use and its association with other psychotropic agents among inpatients with SZ and MDD. Prescription of hypnotic medication was found to be highly frequent, suggesting the presence of an evidence-practice gap. It was revealed that prescription of two or more main antipsychotic agents is commonly associated with the use of hypnotic medication for treatment of SZ and MDD. Further clinical trials of hypnotic medication for psychiatric patients will be needed to adequately address the efficacy of these interventions and improve the clinical guidelines.

Acknowledgement

We would like to thank the individuals that participated in this study.

Funding:

This study was supported by the Japan Agency for Medical Research and Development (AMED) under Grant Number JP16dk0307060, and AMED under Grant Number JP19dk0307083, the Health and Labor Sciences Research Grants (H29-Seishin-Ippan-001, 19GC1201), the Japanese Society of Neuropsychopharmacology, the Japanese Society of Mood Disorders and the Japanese Society of Clinical Neuropsychopharmacology.

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Table1. Percentages of hypnotic medication use in SZ and MDD.

Sex	Age (y)	SZ (n=2146)				MDD (n=1031)			
		N	Number of hypnotic medication ^a			N	Number of hypnotic medication ^a		
			0	1	2+		0	1	2+
Men	0-19	19	57.9%	36.8%	5.3%	12	41.7%	58.3%	0.0%
	20-39	382	49.5%	37.7%	12.8%	46	45.7%	34.8%	19.6%
	40-59	395	40.5%	37.2%	22.3%	145	24.1%	44.1%	31.7%
	60-79	169	36.7%	40.8%	22.5%	137	39.4%	42.3%	18.2%
	80+	9	55.6%	33.3%	11.1%	19	42.1%	42.1%	15.8%
	Total	974	43.8%	38.0%	18.2%	359	34.3%	42.6%	23.1%
Women	0-19	40	55.0%	42.5%	2.5%	23	65.2%	30.4%	4.3%
	20-39	363	49.3%	33.1%	17.6%	89	39.3%	31.5%	29.2%
	40-59	475	36.6%	41.7%	21.7%	181	27.1%	46.4%	26.5%
	60-79	282	44.7%	41.8%	13.5%	311	35.0%	41.8%	23.2%
	80+	12	41.7%	50.0%	8.3%	68	45.6%	42.6%	11.8%
	Total	1172	43.2%	39.2%	17.7%	672	35.6%	41.4%	23.1%
Total		2146	43.5%	38.6%	17.9%	1031	35.1%	41.8%	23.1%

^a: Significant difference among age groups. (χ^2 test, $P < 0.05$)

Table 2. The results of multivariable logistic regression analyses for any hypnotic medication use in SZ.

	Percentage of any hypnotic medication use	Crude			Adjusted				
		OR	95%CI	<i>P</i> -value	OR	95%CI	<i>P</i> -value		
Sex									
Women	56.8%	1.031	0.869	1.224	0.725	1.055	0.882	1.262	0.561
Men	56.1%	1.000				1.000			
Age					<0.001				0.001
0-19y	44.1%	0.769	0.451	1.311		0.814	0.470	1.408	
20-39y	50.6%	1.000				1.000			
40-59y	61.5%	1.561	1.280	1.903		1.508	1.228	1.851	
60-79y	58.3%	1.366	1.079	1.729		1.451	1.132	1.859	
80+y	52.4%	1.074	0.451	2.559		1.519	0.626	3.687	
Study site									
University hospitals	56.8%	1.024	0.860	1.219	0.791	1.111	0.923	1.337	0.266
Other hospitals	56.3%	1.000				1.000			
mECT									
Yes	51.0%	0.796	0.528	1.198	0.274	0.760	0.497	1.164	0.207
No	56.7%	1.000				1.000			
Antipsychotics					<0.001				<0.001
2 or more	66.2%	2.026	1.695	2.420		1.730	1.434	2.088	
1	49.2%	1.000				1.000			

0	50.0%	1.034	0.567	1.888		0.987	0.535	1.820		
Anticholinergic drugs										
Yes	65.3%	1.693	1.398	2.050	<0.001	1.317	1.074	1.615	0.008	
No	52.7%	1.000				1.000				
Antidepressants										
Yes	65.4%	1.507	1.099	2.067	0.011	1.359	0.982	1.882	0.064	
No	55.6%	1.000				1.000				
Anxiolytics										
Yes	64.8%	1.647	1.364	1.990	<0.001	1.449	1.190	1.766	<0.001	
No	52.7%	1.000				1.000				
Mood stabilizers/Antiepileptic drugs										
Yes	65.4%	1.661	1.364	2.024	<0.001	1.496	1.218	1.838	<0.001	
No	53.2%	1.000				1.000				

Explanatory variables in the present study were sex, age, study site, mECT, antipsychotics, antidepressants, anticholinergic drugs, anxiolytics, and mood stabilizers/antiepileptic drugs.

Table 3. The results of multivariable logistic regression analyses for two or more hypnotic medication use in SZ.

	Percentage of 2 or more hypnotic medication use	Crude			Adjusted				
		OR	95%CI	<i>P</i> -value	OR	95%CI	<i>P</i> -value		
Sex									
Women	17.7%	0.977	0.782	1.220	0.837	1.020	0.811	1.283	0.865
Men	18.0%	1.000				1.000			
Age					<0.001				0.005
0-19y	3.4%	0.196	0.047	0.815		0.211	0.051	0.884	
20-39y	15.2%	1.000				1.000			
40-59y	21.8%	1.557	1.204	2.013		1.470	1.130	1.912	
60-79y	16.9%	1.133	0.825	1.557		1.160	0.834	1.613	
80+y	9.5%	0.589	0.135	2.562		0.740	0.168	3.260	
Study site									
University hospitals	16.3%	0.841	0.669	1.057	0.137	0.912	0.718	1.158	0.450
Other hospitals	18.8%	1.000				1.000			
mECT									
Yes	14.6%	0.782	0.439	1.393	0.403	0.815	0.451	1.472	0.497
No	17.9%	1.000				1.000			
Antipsychotics					<0.001				<0.001
2 or more	23.4%	1.903	1.519	2.383		1.625	1.281	2.062	
1	13.8%	1.000				1.000			

0	9.1%	0.624	0.220	1.767		0.613	0.215	1.750	
Anticholinergic drugs									
Yes	22.1%	1.498	1.188	1.888	0.001	1.216	0.949	1.558	0.122
No	16.0%	1.000				1.000			
Antidepressants									
Yes	22.7%	1.399	0.973	2.011	0.070	1.282	0.883	1.861	0.191
No	17.4%	1.000				1.000			
Anxiolytics									
Yes	20.1%	1.246	0.987	1.573	0.065	1.077	0.843	1.376	0.551
No	16.8%	1.000				1.000			
Mood stabilizers/Antiepileptic drugs									
Yes	25.2%	1.902	1.507	2.401	<0.001	1.679	1.320	2.136	<0.001
No	15.1%	1.000				1.000			

Explanatory variables in the present study were sex, age, study site, mECT, antipsychotics, antidepressants, anticholinergic drugs, anxiolytics, and mood stabilizers/antiepileptic drugs.

Table 4. The results of multivariable logistic regression analyses for any hypnotic medication use in MDD.

	Percentage of any hypnotic medication use	Crude			Adjusted				
		OR	95%CI	<i>P</i> -value	OR	95%CI	<i>P</i> -value		
Sex									
Women	64.4%	0.944	0.721	1.236	0.676	1.011	0.762	1.342	0.937
Men	65.7%	1.000				1.000			
Age					<0.001				<0.001
0-19y	42.9%	0.532	0.251	1.128		0.597	0.273	1.304	
20-39y	58.5%	1.000				1.000			
40-59y	74.2%	2.042	1.338	3.117		2.121	1.373	3.277	
60-79y	63.6%	1.239	0.837	1.836		1.506	0.998	2.270	
80+y	55.2%	0.872	0.506	1.503		0.923	0.526	1.619	
Study site									
University hospitals	63.6%	0.852	0.651	1.113	0.240	0.948	0.711	1.265	0.718
Other hospitals	67.2%	1.000				1.000			
mECT									
Yes	52.7%	0.558	0.385	0.810	0.002	0.570	0.383	0.849	0.006
No	66.6%	1.000				1.000			
Antidepressants					<0.001				<0.001
2 or more	75.6%	1.879	1.342	2.632		1.874	1.321	2.657	
1	62.3%	1.000				1.000			

0	59.3%	0.881	0.619	1.253		0.772	0.521	1.146		
Antipsychotics										
Yes	65.5%	1.059	0.820	1.368	0.658	1.049	0.800	1.377	0.727	
No	64.2%	1.000				1.000				
Anticholinergic drugs										
Yes	65.1%	1.011	0.533	1.918	0.974	0.834	0.422	1.650	0.602	
No	64.9%	1.000				1.000				
Anxiolytics										
Yes	73.1%	1.795	1.360	2.369	<0.001	1.631	1.218	2.183	0.001	
No	60.2%	1.000				1.000				
Mood stabilizers/Antiepileptic drugs										
Yes	72.3%	1.515	1.072	2.142	0.019	1.762	1.209	2.570	0.003	
No	63.2%	1.000				1.000				

Explanatory variables in the present study were sex, age, study site, mECT, antipsychotics, antidepressants, anticholinergic drugs, anxiolytics, and mood stabilizers/antiepileptic drugs.

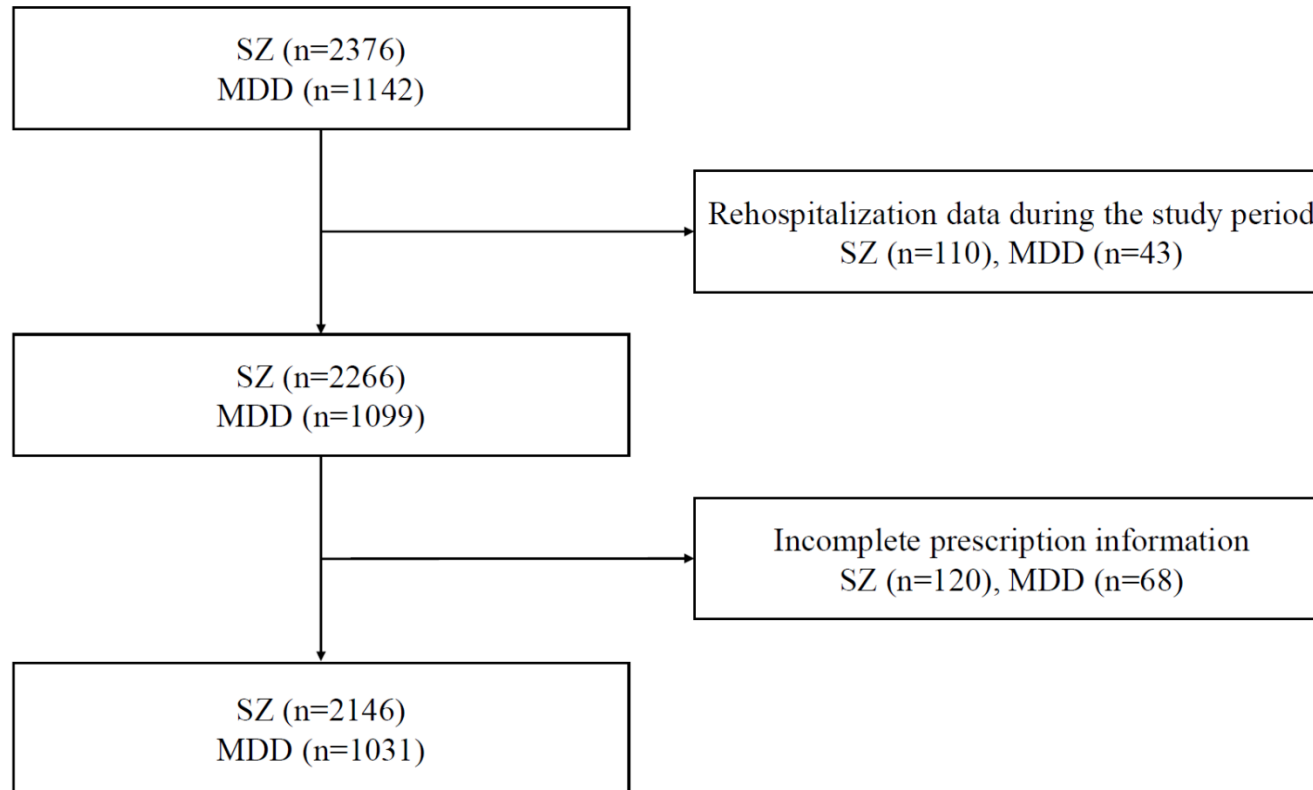
Table 5. The results of multivariable logistic regression analyses for two or more hypnotic medication use in MDD.

	Percentage of 2 or more hypnotic medication use	Crude			Adjusted				
		OR	95%CI	<i>P</i> -value	OR	95%CI	<i>P</i> -value		
Sex									
Women	23.1%	0.997	0.736	1.351	0.984	1.034	0.755	1.418	0.833
Men	23.1%	1.000				1.000			
Age					0.002				0.008
0-19y	2.9%	0.084	0.011	0.637		0.086	0.011	0.664	
20-39y	25.9%	1.000				1.000			
40-59y	28.8%	1.158	0.736	1.822		1.133	0.713	1.801	
60-79y	21.7%	0.790	0.506	1.233		0.892	0.563	1.413	
80+y	12.6%	0.414	0.197	0.867		0.422	0.199	0.896	
Study site									
University hospitals	22.4%	0.901	0.668	1.215	0.496	1.026	0.747	1.409	0.874
Other hospitals	24.3%	1.000				1.000			
mECT									
Yes	17.8%	0.693	0.431	1.116	0.132	0.718	0.436	1.181	0.192
No	23.8%	1.000				1.000			
Antidepressants					0.004				0.004
2 or more	31.1%	1.722	1.232	2.408		1.704	1.205	2.410	
1	20.8%	1.000				1.000			

0	20.4%	0.976	0.636	1.498		0.864	0.542	1.378	
Antipsychotics									
Yes	25.9%	1.395	1.041	1.868	0.026	1.359	1.001	1.845	0.049
No	20.1%	1.000				1.000			
Anticholinergic drugs									
Yes	30.2%	1.469	0.754	2.865	0.258	1.192	0.587	2.423	0.627
No	22.8%	1.000				1.000			
Anxiolytics									
Yes	28.8%	1.627	1.212	2.186	0.001	1.476	1.085	2.007	0.013
No	19.9%	1.000				1.000			
Mood stabilizers/Antiepileptic drugs									
Yes	27.7%	1.360	0.952	1.942	0.091	1.385	0.941	2.038	0.099
No	22.0%	1.000				1.000			

Explanatory variables in the present study were sex, age, study site, mECT, antipsychotics, antidepressants, anticholinergic drugs, anxiolytics, and mood stabilizers/antiepileptic drugs.

Figure1. Patients flow chart



Supplementary Table1. Psychotropic medications analyzed in the study and percentage of each hypnotic medication prescribed.

Hypnotic medications	Generic name	ATC code	SZ (n=2146)		MDD (n=1031)		
			n	%	n	%	
Benzodiazepine derivatives	Flurazepam	N05CD01	4	0.2	1	0.1	
	Nitrazepam	N05CD02	230	10.7	63	6.1	
	Flunitrazepam	N05CD03	485	22.6	187	18.1	
	Estazolam	N05CD04	44	2.1	23	2.2	
	Triazolam	N05CD05	49	2.3	31	3.0	
	Lormetazepam	N05CD06	7	0.3	9	0.9	
	Brotizolam	N05CD09	250	11.6	151	14.6	
	Quazepam	N05CD10	34	1.6	9	0.9	
	Benzodiazepine related drugs	Zopiclone	N05CF01	71	3.3	31	3.0
		Zolpidem	N05CF02	82	3.8	97	9.4
Eszopiclone		N05CF04	103	4.8	78	7.6	
Melatonin receptor agonists	Ramelteon	N05CH02	74	3.4	64	6.2	
Other hypnotics and sedatives	Suvorexant	N05CM19	207	9.6	187	18.1	
Barbiturates	Pentobarbital	N05CA01	0	0.0	0	0.0	
	Amobarbital	N05CA02	0	0.0	1	0.1	
	Barbital	N05CA04	0	0.0	0	0.0	
	Secobarbital	N05CA06	0	0.0	0	0.0	
Aldehydes and derivatives	Chloral hydrate	N05CC01	0	0.0	0	0.0	