

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Comorbid Physical and Psychiatric Disorders and Cox Proportional Hazards Modeling

Comorbid physical and psychiatric disorders considered in this study based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10):

Psychiatric disorders

F0, mental disorders due to known physiological conditions; F1, mental and behavioral disorders due to psychoactive substance use; F2, schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders; F3, mood disorders; F4, anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders; F5, behavioral syndromes associated with physiological disturbances and physical factors; F6, disorders of adult personality and behavior; F7, intellectual disabilities; F8, pervasive and specific developmental disorders; F9, behavioral and emotional disorders with onset usually occurring in childhood and adolescence.

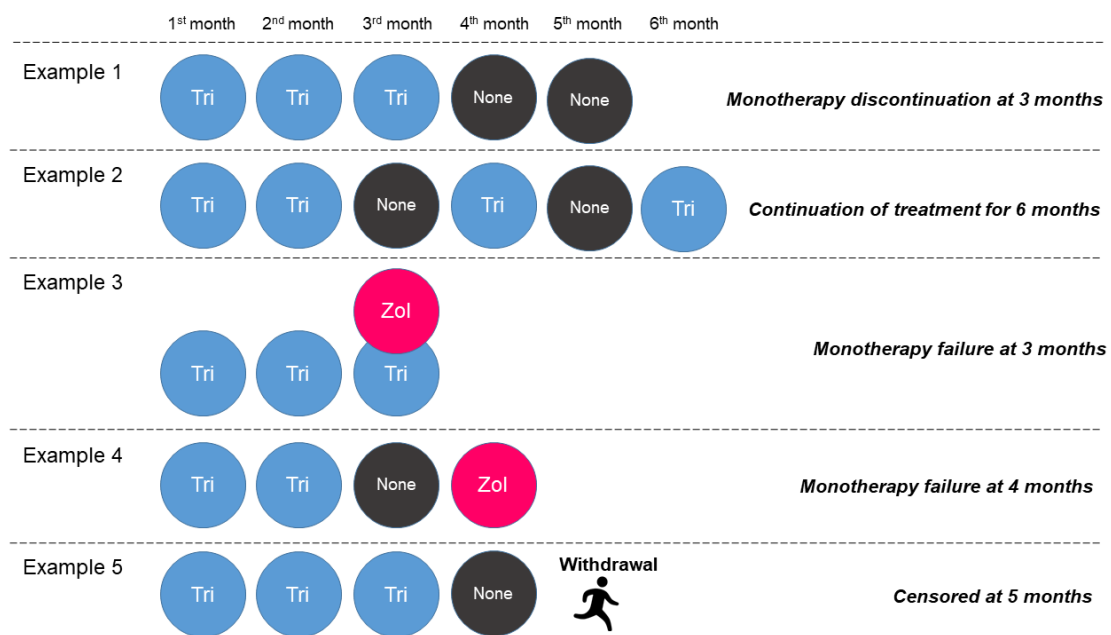
Physical disorders

Hypertension, hyperlipidemia, diabetes mellitus, cancer, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, bronchial asthma, chronic obstructive pulmonary disease, coronary artery disease, pulmonary embolism, deep vein thrombosis, hypothyroidism, subarachnoid hemorrhage, nontraumatic intracerebral hemorrhage, cerebral infarction, heart failure, and inflammatory bowel disease.

Testing the Cox proportional hazards modeling assumptions:

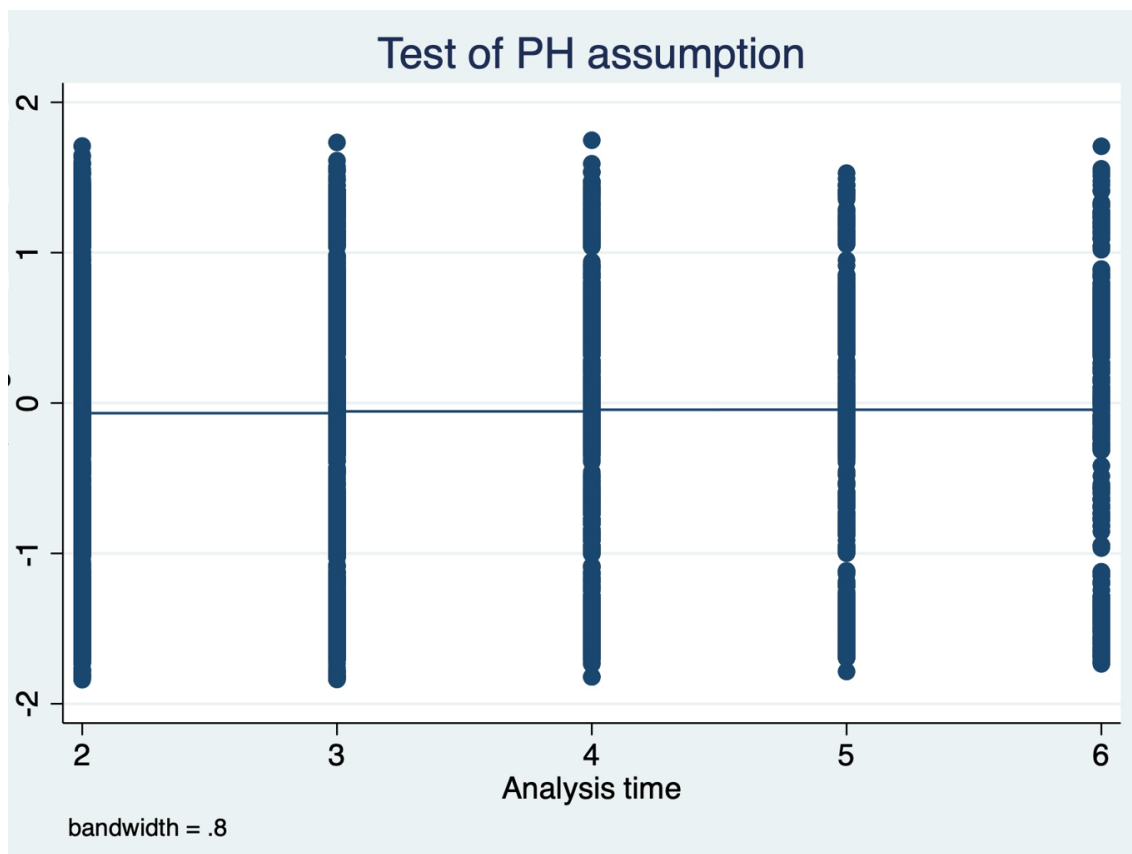
The Cox proportional hazards model assumptions were tested using the STATA procedure 'estat phtest' (STATA 13.0; Stata Corp, College Station, TX) and by plotting Schoenfeld residuals against time-period of the first prescription of hypnotics. There was no evidence of deviation from proportional hazards for time-period ($p > 0.05$, with no apparent slope in the residual plots) (eFigure 1). Therefore, a proportional hazard was established.

eFigure 1. Specific Examples of Monotherapy Failure or Monotherapy Discontinuation Events

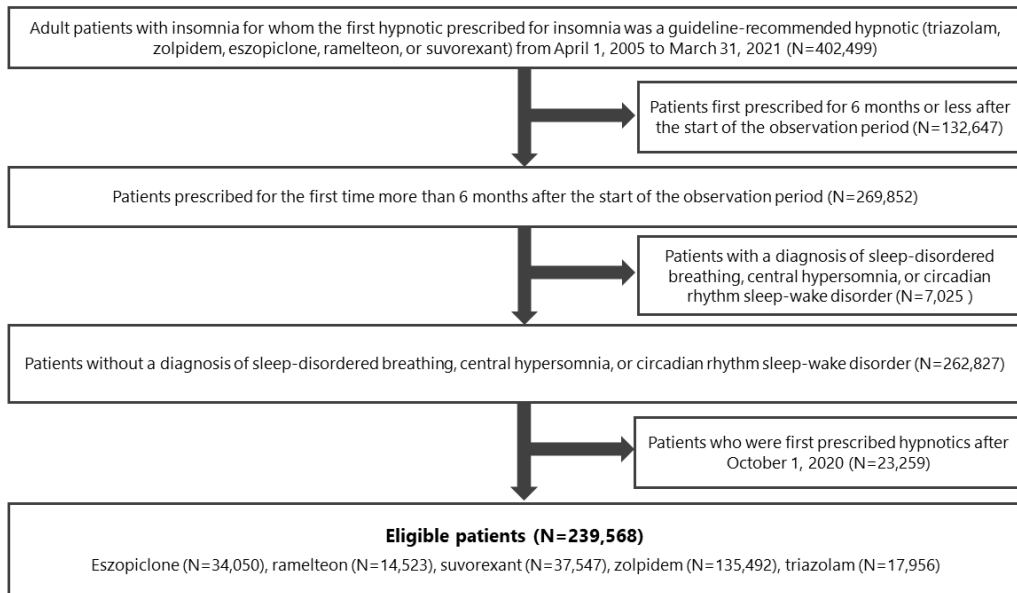


Abbreviations: Tri, triazolam; Zol, zolpidem

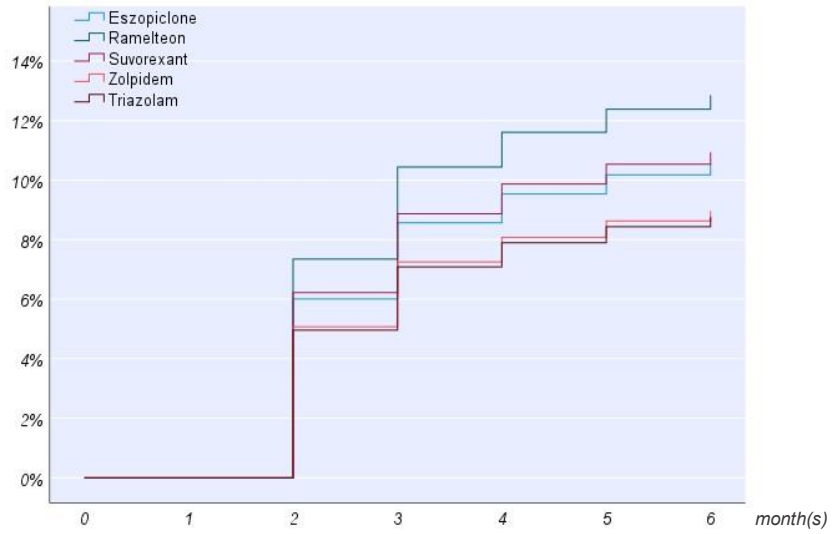
eFigure 2. Assumptions of the Cox Proportional Hazards Regression Model



eFigure 3. Participant Selection Flowchart



eFigure 4. Cox Proportional Hazards Regression Analysis for Monotherapy Failure



eTable 1. List of Hypnotics Covered by Insurance in Japan

Generic name	ATC code	Introduction
Benzodiazepine		
Brotizolam	N05CD09	Prior to 2005
Estazolam	N05CD04	Prior to 2005
Etizolam	N05BA19	Prior to 2005
Flunitrazepam	N05CD03	Prior to 2005
Flurazepam	N05CD01	Prior to 2005
Haloxazolam	—	Prior to 2005
Lormetazepam	N05CD06	Prior to 2005
Nimetazepam	N05CD15	Prior to 2005
Nitrazepam	N05CD02	Prior to 2005
Quazepam	N05CD10	Prior to 2005
Rilmazafone	—	Prior to 2005
Triazolam	N05CD05	Prior to 2005
Non-benzodiazepine		
Eszopiclone	N05CF04	April 2012
Zolpidem	N05CF02	Prior to 2005
Zopiclone	N05CF01	Prior to 2005
Melatonin receptor agonist		
Melatonin ^A	N05CH01	June 2020
Ramelteon	N05CH02	July 2010
Orexin receptor antagonist		
Lemborexant	—	June 2020
Suvorexant	N05CM19	November 2014

Note: ^AInsurance coverage is available for difficulty falling asleep associated with childhood neurodevelopmental disorders.

Abbreviation: ATC, Anatomical Therapeutic Chemical classification 2021

eTable 2. List of Anxiolytics Covered by Insurance in Japan

Generic name	ATC code
Alprazolam	N05BA12
Bromazepam	N05BA08
Chlordiazepoxide	N05BA02
Clorazepate	N05BA05
Clotiazepam	N05BA21
Cloxazolam	N05BA22
Diazepam	N05BA01
Etizolam	N05BA19
Fludiazepam	N05BA17
Flutazolam	—
Flutoprazepam	—
Hydroxyzine	N05BB01
Loflazepate	N05BA18
Lorazepam	N05BA06
Medazepam	N05BA03
Mexazolam	N05BA25
Oxazepam	N05BA04
Oxazolam	—
Prazepam	N05BA11
Tandospirone	—
Tofisopam	N05BA23

ATC, Anatomical Therapeutic Chemical classification 2021

eTable 3. List of Antidepressants Covered by Insurance in Japan

Generic name	ATC code
Amitriptyline	N06AA09
Amoxapine	N06AA17
Clomipramine	N06AA04
Desipramine	N06AA01
Dosulepin	N06AA16
Duloxetine	N06AX21
Escitalopram	N06AB10
Fluvoxamine	N06AB08
Imipramine	N06AA02
Lofepramine	N06AA07
Maprotiline	N06AA21
Mianserin	N06AX03
Milnacipran	N06AX17
Mirtazapine	N06AX11
Nortriptyline	N06AA10
Paroxetine	N06AB05
Safrazine	—
Sertraline	N06AB06
Setiptiline	—
Sulpiride	N05AL01
Trazodone	N06AX05
Trimipramine	N06AA06
Venlafaxine	N06AX16
Vortioxetine	N06AX26

ATC, Anatomical Therapeutic Chemical classification 2021

eTable 4. List of Antipsychotics Covered by Insurance in Japan

Generic name	ATC code
Aripiprazole	N05AX12
Asenapine	N05AH05
Blonanserin	—
Blonanserin (tape)	—
Brexpiprazole	N05AX16
Bromperidol	N05AD06
Carpipramine	—
Chlorpromazine	N05AA01
Clocapramine	—
Clozapine	N05AH02
Floropipamide	—
Fluphenazine	N05AB02
Haloperidol	N05AD01
Levomepromazine	N05AA02
Lurasidone	N05AE05
Moperone	N05AD04
Mosapramine	N05AX10
Nemonapride	—
Olanzapine	N05AH03
Oxypertine	N05AE01
Paliperidone	N05AX13
Perospirone	—
Perphenazine	N05AB03
Pimozide	N05AG02
Prochlorperazine	N05AB04
Propericyazine	—
Quetiapine	N05AH04
Risperidone	N05AX08
Siperone	—
Sulpiride	N05AL01
Sultopride	N05AL02
Tiapride	N05AL03
Thioridazine	N05AC02
Timiperone [†]	—
Trifluoperazine	N05AB06
Zotepine	N05AX11

ATC, Anatomical Therapeutic Chemical classification 2021

eTable 5. Crude and Adjusted Cox Proportional Hazards Regression Analysis

	cHR (95% CI) ^a	P-value	aHR (95% CI) ^{a,b}	P-value
Guideline-recommended hypnotic				
Eszopiclone	1 [Reference]		1 [Reference]	
Ramelteon	1.28 (1.22–1.35)	<.001 ^d	1.23 (1.17–1.30)	<.001 ^d
Suvorexant	1.07 (1.03–1.12)	.002 ^c	1.04 (0.99–1.08)	.091
Zolpidem	0.74 (0.71–0.76)	<.001 ^d	0.84 (0.81–0.87)	<.001 ^d
Triazolam	0.78 (0.74–0.83)	<.001 ^d	0.82 (0.78–0.87)	<.001 ^d
Age group				
20–39 years	1 [Reference]		1 [Reference]	
40–64 years	0.75 (0.73–0.77)	<.001 ^d	0.88 (0.86–0.91)	<.001 ^d
65 years or more	0.64 (0.60–0.68)	<.001 ^d	0.85 (0.80–0.90)	<.001 ^d
Sex				
Male	1 [Reference]		1 [Reference]	
Female	0.84 (0.82–0.86)	<.001 ^d	0.90 (0.88–0.93)	<.001 ^d
Prescription instruction				
As-needed only	1 [Reference]		1 [Reference]	
Regular	1.64 (1.59–1.69)	<.001 ^d	1.45 (1.41–1.50)	<.001 ^d
Physical comorbidities				
Hypertension	0.84 (0.81–0.87)	<.001 ^d	1.02 (0.98–1.06)	.36
Hyperlipidemia	0.86 (0.83–0.89)	<.001 ^d	0.99 (0.95–1.04)	.73
Diabetes	0.88 (0.85–0.92)	<.001 ^d	1.03 (0.98–1.08)	.32
Cancer	0.93 (0.88–0.97)	.002 ^c	1.37 (1.30–1.44)	<.001 ^d
Rheumatoid arthritis	0.90 (0.79–1.02)	.10	1.08 (0.95–1.23)	.24
Parkinson's disease	1.39 (1.19–1.62)	<.001 ^d	1.09 (0.93–1.28)	.28
Multiple sclerosis	0.89 (0.57–1.38)	.59	1.16 (0.75–1.80)	.50
Asthma	0.91 (0.86–0.96)	<.001 ^d	1.01 (0.96–1.07)	.61
Chronic obstructive pulmonary disease	1.08 (0.92–1.26)	.34	1.20 (1.02–1.41)	.03 ^c
Coronary artery disease	0.89 (0.83–0.95)	<.001 ^d	1.01 (0.94–1.09)	.82
Pulmonary embolism	1.06 (0.76–1.47)	.74	1.19 (0.85–1.66)	.32
Deep vein thrombosis	0.82 (0.70–0.96)	.02 ^c	0.97 (0.82–1.14)	.67
Hypothyroid	1.09 (0.98–1.21)	.12	1.10 (0.99–1.22)	.08
Subarachnoid hemorrhage	1.04 (0.80–1.34)	.78	1.31 (1.01–1.70)	.04 ^c
Nontraumatic intracerebral hemorrhage	1.06 (0.86–1.31)	.57	1.30 (1.06–1.61)	.01 ^c

Cerebral infarction	1.01 (0.91–1.13)	.82	1.20 (1.07–1.34)	.001*
Heart failure	1.00 (0.93–1.07)	1.00	1.19 (1.10–1.28)	<.001 ^d
Inflammatory bowel disease	1.04 (0.88–1.23)	.69	1.23 (1.04–1.46)	.02 ^c
Psychiatric comorbidities				
Organic mental disorder	1.18 (0.99–1.40)	.07	1.01 (0.84–1.20)	.96
Substance use disorder	1.34 (1.18–1.53)	<.001 ^d	1.23 (1.08–1.41)	.002 ^c
Schizophrenia	1.64 (1.55–1.74)	<.001 ^d	1.00 (0.93–1.08)	.95
Mood disorders	2.21 (2.15–2.26)	<.001 ^d	1.47 (1.41–1.53)	<.001 ^d
Anxiety disorder	1.76 (1.71–1.80)	<.001 ^d	1.28 (1.25–1.32)	<.001 ^d
Behavioral and emotional disorders	1.59 (1.46–1.72)	<.001 ^d	1.20 (1.10–1.30)	<.001 ^d
Personality disorder	1.88 (1.50–2.35)	<.001 ^d	1.26 (1.00–1.57)	.046 ^c
Intellectual disability	1.12 (0.85–1.48)	.43	0.88 (0.66–1.16)	.36
Psychological development disorder	1.35 (1.19–1.54)	<.001 ^d	0.87 (0.75–1.00)	.04 ^c
BEDCA and UMD	1.74 (1.58–1.93)	<.001 ^d	1.25 (1.13–1.39)	<.001 ^{**}
Psychotropic medications				
Antidepressants	2.14 (2.09–2.20)	<.001 ^d	1.24 (1.19–1.30)	<.001 ^d
Anxiolytics	1.82 (1.77–1.87)	<.001 ^d	1.25 (1.21–1.29)	.001 ^c
Antipsychotics	1.66 (1.59–1.74)	<.001 ^d	1.24 (1.16–1.32)	<.001 ^d

Note:

^a Large hazard ratios indicate more monotherapy failures, whereas small hazard ratios indicate fewer monotherapy failures.

^b Adjusted for age group (20–39, 40–64, ≥65 years), sex, administration instructions of the first prescribed hypnotic (as-needed only or regular prescription), concomitant anxiolytics, concomitant antidepressants, concomitant antipsychotics, comorbid psychiatric disorders, and comorbid physical disorders in the month of the first prescription.

^c P-value <.05

^d P-value <.001

Abbreviations: aHR, adjusted hazard ratio; BEDCA, behavioral and emotional disorders with onset usually occurring in childhood and adolescence; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CHR, crude hazard ratio; UMD, unspecified mental disorder

eTable 6. Sensitivity Analyses of Cox Proportional Hazards Regression Analysis

	Adjusted HR (95%CI) ^{a,b}	P-value
<i>Under 64 years old^c</i>		
Eszopiclone	1 [Reference]	
Ramelteon	1.21 (1.15–1.28)	<.001 ^k
Suvorexant	1.04 (0.99–1.08)	.12
Zolpidem	0.84 (0.80–0.87)	<.001 ^k
Triazolam	0.82 (0.77–0.87)	<.001 ^k
<i>Without mood disorder^d</i>		
Eszopiclone	1 [Reference]	
Ramelteon	1.24 (1.15–1.33)	<.001 ^k
Suvorexant	1.05 (0.99–1.11)	.12
Zolpidem	0.80 (0.77–0.84)	<.001 ^k
Triazolam	0.77 (0.71–0.83)	<.001 ^k
<i>Without anxiety disorder^e</i>		
Eszopiclone	1 [Reference]	
Ramelteon	1.28 (1.20–1.37)	<.001 ^k
Suvorexant	1.06 (1.01–1.12)	.03 ^j
Zolpidem	0.84 (0.80–0.88)	<.001 ^k
Triazolam	0.83 (0.78–0.90)	<.001 ^k
<i>Without mood or anxiety disorder^f</i>		
Eszopiclone	1 [Reference]	
Ramelteon	1.34 (1.23–1.47)	<.001 ^k
Suvorexant	1.09 (1.01–1.17)	.02 ⁱ
Zolpidem	0.80 (0.75–0.85)	<.001 ^k
Triazolam	0.77 (0.70–0.85)	<.001 ^k
<i>Without any psychiatric disorder^g</i>		
Eszopiclone	1 [Reference]	
Ramelteon	1.32 (1.20–1.45)	<.001 ^k
Suvorexant	1.10 (1.02–1.18)	.02 ⁱ
Zolpidem	0.79 (0.75–0.84)	<.001 ^k
Triazolam	0.75 (0.68–0.83)	<.001 ^k
<i>Monotherapy failure considering trazodone^h</i>		
Eszopiclone	1 [Reference]	
Ramelteon	1.23 (1.17–1.30)	<.001 ^k
Suvorexant	1.06 (1.02–1.10)	.008 ^j
Zolpidem	0.84 (0.81–0.87)	<.001 ^k
Triazolam	0.81 (0.76–0.85)	<.001 ^k

After November 2014ⁱ

Eszopiclone	1 [Reference]	
Ramelteon	1.24 (1.18–1.31)	<.001 ^k
Suvorexant	1.04 (0.99–1.08)	.10
Zolpidem	0.83 (0.80–0.87)	<.001 ^k
Triazolam	0.80 (0.75–0.85)	<.001 ^k

Note:

^a Large hazard ratios indicate more monotherapy failures, whereas small hazard ratios indicate fewer monotherapy failures.

^b Adjusted for age group (20–39, 40–64, ≥65 years), sex, administration instructions of the first prescribed hypnotic (as-needed only or regular prescription), concomitant anxiolytics, concomitant antidepressants, concomitant antipsychotics, comorbid psychiatric disorders, and comorbid physical disorders in the month of the first prescription.

^c Sensitivity analysis in patients under 64 years of age prescribed guideline-recommended sleep medications for the first time.

^d Sensitivity analysis in patients without mood disorder

^e Sensitivity analysis in patients without anxiety disorder

^f Sensitivity analysis in patients without mood or anxiety disorder

^g Sensitivity analysis in patients without any psychiatric disorder

^h Sensitivity analysis of monotherapy failure considering trazodone

ⁱ Sensitivity analysis of patients who were first prescribed hypnotics after November 2014, when all guideline-recommended hypnotics became available for prescription in Japan.

^j P-value <.05

^k P-value <.001

Abbreviations: CI, confidence interval; HR, hazard ratio

eTable 7. Events Occurring Within 6 Months of First Prescription of Guideline-Recommended Hypnotics Among Patients Without Failure of Guideline-Recommended Hypnotic Monotherapy

	Eszopiclone	Ramelteon	Suvorexant	Zolpidem	Triazolam	Total
	N=29,988	N=12,330	N=32,780	N=123,426	N=16,266	N=214,790
Monotherapy discontinuation	24,857 (82.9%)	10,468 (84.9%)	27,538 (84.0%)	105,138 (85.2%)	13,622 (83.7%)	181,623 (84.6%)
Continuation for 6 months	3,627 (12.1%)	1,268 (10.3%)	3,564 (10.9%)	12,915 (10.5%)	1,897 (11.7%)	23,271 (10.8%)
Censor	1,504 (5.0%)	594 (4.8%)	1,678 (5.1%)	5,373 (4.4%)	747 (4.6%)	9,896 (4.6%)

eTable 8. Crude and Adjusted Logistic Regression Analyses

	cOR (95% CI) ^a	P-value	aOR (95% CI) ^{a,b}	P-value
Guideline-recommended hypnotic				
Eszopiclone	1 [Reference]		1 [Reference]	
Ramelteon	1.16 (1.10–1.23)	<.001 ^d	1.31 (1.24–1.40)	<.001 ^d
Suvorexant	1.08 (1.04–1.13)	<.001 ^d	1.20 (1.15–1.26)	<.001 ^d
Zolpidem	1.19 (1.15–1.23)	<.001 ^d	1.00 (0.97–1.04)	.97
Triazolam	1.06 (1.01–1.12)	.02 ^c	1.02 (0.97–1.07)	.50
Age group				
20–39 years	1 [Reference]		1 [Reference]	
40–64 years	1.08 (1.06–1.11)	<.001 ^d	0.92 (0.90–0.95)	<.001 ^d
65 years or more	0.84 (0.80–0.87)	<.001 ^d	0.65 (0.62–0.69)	<.001 ^d
Sex				
Male	1 [Reference]		1 [Reference]	
Female	1.19 (1.16–1.22)	<.001 ^d	1.09 (1.06–1.11)	<.001 ^d
Prescription instruction				
As-needed only	1 [Reference]		1 [Reference]	
Regular	0.48 (0.47–0.50)	<.001 ^d	0.51 (0.49–0.52)	<.001 ^d
Physical comorbidities				
Hypertension	0.79 (0.77–0.82)	<.001 ^d	0.70 (0.68–0.73)	<.001 ^d
Hyperlipidemia	0.84 (0.81–0.86)	<.001 ^d	0.88 (0.84–0.91)	<.001 ^d
Diabetes	0.83 (0.80–0.86)	<.001 ^d	0.86 (0.83–0.90)	<.001 ^d
Cancer	1.18 (1.13–1.24)	<.001 ^d	0.86 (0.82–0.90)	<.001 ^d
Rheumatoid arthritis	0.92 (0.82–1.03)	.14	0.84 (0.75–0.95)	.003 ^c
Parkinson's disease	0.43 (0.37–0.49)	<.001 ^d	0.63 (0.54–0.73)	<.001 ^d
Multiple sclerosis	1.10 (0.74–1.65)	.63	0.79 (0.52–1.19)	.25
Asthma	1.03 (0.98–1.08)	.23	0.99 (0.94–1.05)	.81
Chronic obstructive pulmonary disease	0.99 (0.85–1.15)	.86	1.00 (0.85–1.17)	.99
Coronary artery disease	1.08 (1.01–1.15)	.02 ^c	1.23 (1.15–1.32)	<.001 ^d
Pulmonary embolism	0.98 (0.72–1.33)	.88	0.76 (0.55–1.05)	.09
Deep vein thrombosis	1.44 (1.24–1.68)	<.001 ^d	1.27 (1.08–1.49)	.004 ^c
Hypothyroid	0.89 (0.81–0.98)	.02 ^c	0.96 (0.87–1.07)	.48
Subarachnoid hemorrhage	2.15 (1.54–3.00)	<.001 ^d	2.01 (1.43–2.82)	<.001 ^d
Nontraumatic intracerebral hemorrhage	1.23 (0.99–1.53)	.06	1.25 (1.00–1.56)	.06
Cerebral infarction	0.87 (0.79–0.96)	.004 ^c	0.94 (0.84–1.04)	.20

Heart failure	1.01 (0.94–1.08)	.87	1.00 (0.93–1.08)	.92
Inflammatory bowel disease	1.02 (0.87–1.20)	.80	0.79 (0.67–0.94)	.006 ^c
Psychiatric comorbidities				
Organic mental disorder	0.64 (0.55–0.75)	<.001 ^d	0.76 (0.65–0.90)	.001 ^c
Substance use disorder	0.81 (0.71–0.92)	.002 ^c	0.90 (0.78–1.03)	.12
Schizophrenia	0.44 (0.42–0.47)	<.001 ^d	0.80 (0.75–0.87)	<.001 ^d
Mood disorders	0.40 (0.39–0.41)	<.001 ^d	0.60 (0.58–0.63)	<.001 ^d
Anxiety disorder	0.57 (0.55–0.58)	<.001 ^d	0.76 (0.73–0.78)	<.001 ^d
Behavioral and emotional disorders	0.64 (0.59–0.70)	<.001 ^d	0.88 (0.81–0.97)	.006 ^c
Personality disorder	0.57 (0.45–0.74)	<.001 ^d	0.89 (0.69–1.15)	.38
Intellectual disability	0.49 (0.39–0.61)	<.001 ^d	0.59 (0.47–0.76)	<.001 ^d
Psychological development disorder	0.48 (0.43–0.54)	<.001 ^d	0.70 (0.62–0.80)	<.001 ^d
BEDCA and UMD	0.49 (0.44–0.55)	<.001 ^d	0.68 (0.61–0.77)	<.001 ^d
Psychotropic medications				
Antidepressants	0.39 (0.38–0.40)	<.001 ^d	0.67 (0.64–0.69)	<.001 ^d
Anxiolytics	0.48 (0.45–0.50)	<.001 ^d	0.82 (0.79–0.84)	<.001 ^d
Antipsychotics	0.52 (0.51–0.53)	<.001 ^d	0.67 (0.63–0.72)	<.001 ^d

Note:

^a Large odds ratios indicate more successful discontinuations, whereas small odds ratios indicate fewer successful discontinuations.

^b Adjusted for age group (20–39, 40–64, ≥65 years), sex, administration instructions of the first prescribed hypnotic (as-needed only or regular prescription), concomitant anxiolytics, concomitant antidepressants, concomitant antipsychotics, comorbid psychiatric disorders, and comorbid physical disorders in the month of the first prescription.

^c P-value <.05

^d P-value <.001

Abbreviations: aOR, adjusted odds ratio; BEDCA, behavioral and emotional disorders with onset usually occurring in childhood and adolescence; CI, confidence interval; cOR, crude odds ratio; UMD, unspecified mental disorder