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ORIGINAL RESEARCH

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Evaluation of prescribing patterns of switching to and add-on lemborexant in patients treated with hypnotic medication: a nationwide claims database study in Japan

Sachiko Tanaka-Mizuno [a,b], Kenichi Fujimoto[c], Kazuo Mishima[d], Yukinori Sakata[c], Toshiki Fukasawa[a,e], Kayoko Mizuno[a,e], Satomi Yoshida[a,f], Mika Ishii[c], Takehiro Taninaga[c], Naoki Kubota[c], Margaret Moline[g] and Koji Kawakami[a]

[a]Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan; [b]Laboratory of Epidemiology and Prevention, Kobe Pharmaceutical University, Kobe, Japan; [c]Eisai Co. Ltd, Tokyo, Japan; [d]Department of Neuropsychiatry, Akita University Graduate School of Medicine, Akita, Japan; [e]Department of Digital Health and Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan; [f]Division of Social Medicine, Department of Clinical Medicine, Institute of Medicine, University of Tsukuba, Tsukuba, Japan; [g]Eisai Inc, NJ, USA

ABSTRACT

Background: When considering changing hypnotic pharmacotherapy, lemborexant has attracted attention as a candidate due to its effectiveness and safety profile. However, few studies have investigated switching patterns in clinical practice.

Research design and methods: We conducted a retrospective cohort study using a nationwide claims database. Patients prescribed a single hypnotic who either subsequently switched to (switching cohort) or were additionally prescribed (add-on cohort) lemborexant between July 2020 and December 2021 were identified. Proportion of successful switching was defined as remaining on lemborexant alone or without any hypnotic at 6 months after lemborexant initiation.

Results: The success proportion was 70.1% in the switching cohort ($n = 4,861$) and 38.6% in the add-on cohort ($n = 9,423$). In the add-on cohort, the success proportion was lower in patients with a hypnotic history of ≥180 days (31.4%) and in patients whose prescribed hypnotic was a benzodiazepine or non-benzodiazepine (31.5% and 37.6%, respectively).

Conclusion: The proportion of successful switching was higher in patients who switched to lemborexant than in those who added lemborexant as a concomitant treatment. The lower success proportion in the add-on cohort might be related to clinically more severe insomnia, and/or a concomitant prescription of benzodiazepine or non-benzodiazepine, from which discontinuation may be challenging.

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KEYWORDS
Add-on treatment; hypnotics; lemborexant; prescription pattern; switching

1. Introduction

Insomnia is a common sleep disorder that reportedly affects around 20% of the general population [1,2]. The prevalence of insomnia in Japan is estimated to 13.5% [3]. In Japan, pharmacotherapy is the primary choice of treatment for insomnia [4]. Benzodiazepines (BZDs) and non-benzodiazepine hypnotics, also known as Z-drugs (non-BZDs), have long been used as mainstream drugs. In recent years, however, several new drug classes have been launched, including melatonin receptor agonists (MRA) such as ramelteon (2000), and dual orexin receptor antagonists (DORAs) such as suvorexant (2014) and lemborexant (LEM) (2020). In clinical practice in Japan, although BZDs remain the most prescribed drugs among hypnotics [5], several adverse consequences of BZD use have been reported, including cognitive dysfunction, bone fracture, and overprescription or drug dependence [6–8]. Non-BZDs, which are the second-most prescribed hypnotics [5], have also been associated with disadvantages such as bone fracture, drug dependence, and mortality [9,10]. Therefore, guidance from insomnia experts recommends that BZDs and non-BZDs should be used for short periods, either by switching to other hypnotics or substituting them in place of other hypnotics [4].

Insomnia is defined by the presence of nocturnal insomnia symptoms and associated daytime impairment [11,12]. The goal in the pharmacological treatment of insomnia is the improvement of these nocturnal and daytime complaints, followed by an exit strategy that should include dose reduction, discontinuation, or safe long-term maintenance therapy. Two network meta-analyses comparing all hypnotics suggested that LEM was the most effective, especially for long-term treatment, and had a similar safety profile to other hypnotics [13,14]. In addition, a cost-effectiveness analysis that compared zolpidem, a common non-BZD, suvorexant, and LEM reported that LEM was the more cost-effective drug [15]. Against this background, LEM has become a first-line

CONTACT Sachiko Tanaka-Mizuno tanaka.sachiko.88s@st.kyoto-u.ac.jp Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshidakonoe-Cho, Sakyo-Ku, Kyoto 606-8501, Japan

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drug in pharmacotherapy with guidance from insomnia experts in Japan [4]. Additionally, for patients treated with BZDs, it is recommended that BZDs be reduced or discontinued while switching to LEM.

Although several studies have examined patients who switched from BZDs to LEM [16–19], these were small-scale, and no study has yet examined long-term treatment patterns after switching to LEM. Additionally, little attention has been given to the difference in prescription patterns between switching and add-on strategies. The disadvantages and cost-ineffectiveness of long-term use of drugs with a lesser safety profile warrant evaluation of the actual status of treatment with switching to or adding on LEM in clinical practice.

Here, using a nationwide large-scale claims database, we evaluated prescription patterns among patients treated with other hypnotics who were switched to LEM. Specifically, we sought to describe prescription patterns when LEM was initiated by either switching from or adding to the existing hypnotic. We also evaluated the proportion of patients who had successfully switched to LEM at 6 months after LEM initiation.

2. Patients and methods

2.1. Data source and setting

We used a large-scale nationwide claims database provided by JMDC Inc. (Tokyo, Japan). This database includes information on demographics, hospitalization, inpatient and outpatient treatment, disease diagnosis, procedure treatments, drug prescription, and health checkup results sourced from multiple health insurance societies in Japan [20,21]. The information is based on the membership records of health insurance, making it possible to track enrollees across hospital transfers and visits to multiple medical institutions. Data have been collected since 2005 and as of the end of 2023, the total number of participants was approximately 16 million. The database has been used in multiple epidemiological studies in Japan [22,23]. This study protocol was approved by the Ethics Committees of Kyoto University Graduate School and Faculty of Medicine (No. R3713).

2.2. Study design and patients

We conducted a retrospective cohort study using an existing claims database. Patients satisfying the following criteria were extracted: (a) at least one prescription date for LEM (Anatomical Therapeutic Chemical [ATC] code: N05CM21) between 6 July 2020, the date of launch of LEM, and 31 December 2021, with the date of first prescription during this period regarded as the index date [Day 0]; (b) continuous enrollment in the database for 180 days prior to Day 0; and (c) able to be followed-up for 180 days after Day 0.

From the above patient population, three patient cohorts were further classified by the prescription pattern of hypnotic drugs other than LEM at Day 0. First, patients who switched to LEM from another hypnotic drug were defined as the 'switching cohort.' This cohort included patients who 1) were confirmed to have been prescribed a single hypnotic drug between Day −30 and Day −1; and 2) discontinued the preceding hypnotic drug when LEM was initially prescribed at Day 0. Second, patients who were prescribed LEM in addition to the existing hypnotic drug were defined as the 'add-on cohort.' This cohort included patients who 1) were confirmed to have been prescribed a single hypnotic drug between Day −30 and Day −1, and 2) continued using that preceding hypnotic drug even after LEM prescription was initiated at Day 0. Third, as a reference, patients who were not prescribed any hypnotic drug other than LEM between Day −180 and Day 0 were defined as the 'naive cohort.' In this study, the switching and add-on cohorts were defined only when the preceding hypnotic drug was a single drug; patients who used two or more concomitant hypnotics between Day −30 and Day −1 were excluded.

2.3. Outcome

The primary endpoint was the proportion of patients who successfully switched to LEM at Day 180, defined as follows. The follow-up period was defined as the period from Day 0 to Day 180; if LEM was prescribed as monotherapy or no hypnotic was prescribed during days Day 180–210, the case was defined as successful switching; otherwise, if any other hypnotic drug was prescribed, either in place of or in addition to LEM, the case was defined as unsuccessful (failed) switching. If the prescription of LEM was discontinued before Day 180, that date of discontinuation was considered the final date of LEM prescription, and successful switching was determined to be on the final date of LEM prescription as an alternative to Day 180. Continuation of LEM prescription was specified when no gap lasting more than 30 days was present (Supplementary materials 1).

Secondary endpoints were the success proportions of switching at Day 30 and Day 60, and prescription patterns of hypnotics during the follow-up period, including discontinuation/addition, dose, period, and potency.

2.4. Measurements

Collected background factors were age, sex, comorbidities (depression, schizophrenia spectrum disorders, hypertension, diabetes, chronic liver disease, asthma, obstructive sleep apnea syndrome, and Charlson Comorbidity Index [24]), previous medical history (antidepressants, anxiolytics, antipsychotics, analgesics, antihypertensive drugs, antiepileptic drugs, and opioids), prescription history of hypnotics other than LEM, and prescription history of psychotropic drugs. The hypnotic drug used between Day −30 and Day −1 in the switching cohort and the concomitant hypnotic drug used at Day 0 in the add-on cohort were collectively termed 'the pre-index hypnotic.' These pre-index hypnotics comprised 15 drugs: 10 BZDs, 3 non-BZDs, ramelteon (MRA), and suvorexant (DORA) (Supplementary materials 2). Concomitant drugs other than hypnotics on Day 0, namely antihypertensive and psychotropic drugs and psychotropic drugs that affect insomnia, were separately investigated. Disease information was extracted based on the International Classification of Diseases, Tenth

Revision (ICD-10) codes, and drug information based on ATC codes.

We evaluated the prescription patterns of LEM and other hypnotics at Day 0 and during the follow-up period. Based on the prescription duration and dose of each dispensing, the total period of prescription without discontinuation, flunitrazepam-equivalent daily dose, and potency for 30 days were calculated. Potency was defined as the value calculated by multiplying the flunitrazepam-equivalent dose and the number of days for 30 days, divided by 30. To evaluate regular use, potency >0.8 was defined as regular, and potency ≤ 0.8 was defined as as-needed, respectively.

2.5. Statistical analysis

In this study, patients were classified into three cohorts according to the other hypnotic drug at Day 0 – a switching, add-on, and naive cohort – and statistical analysis was conducted for each cohort separately. Demographics, clinical characteristics, comorbidities, and concomitant drugs were described using summary statistics. The class of the pre-index hypnotic drug between Day −30 and Day −1 was also described. Continuous variables were described as means and standard deviations, and categorical variables were described as numbers and proportions. The prescription patterns of LEM including initial dose and total prescribed duration were also summarized. For the add-on cohort, the tapering period of dose reduction until LEM single use was described. The success proportion of switching at Day 180 was evaluated for each cohort. The patterns of success and failure to switching at Day 30, Day 90, and Day 180 were illustrated using Sankey diagram. Subgroup analysis was conducted for the four pre-index hypnotic categories (BZDs, non-BZDs, MRA, and DORA), hypnotic potency (regular and as-needed), psychotropic use, sex, and age groups. As the explanatory analysis, logistic regression was conducted to evaluate the relationship between the successful switching and background factors. Univariable analysis was first performed with one covariate, and multivariable analysis was subsequently performed with all variables whose confidence intervals did not include one in univariate analysis. R version 4.3.1 (R Foundation) was used for drawing Sankey diagram and SAS version 9.4 (SAS Institute Inc.) was used for all other analyses.

3. Results

3.1. Baseline characteristics

We identified 38,022 patients who met the inclusion criteria (Figure 1). The number in the switching, add-on, and naive cohorts was 4,861, 9,423, and 23,738, respectively. Table 1 describes summary statistics for baseline and clinical characteristics. Mean ± SD of age was 41.8 ± 14.7, 43.8 ± 13.7, and 40.6 ± 14.2 years, and the proportions of males were 48.4%, 49.8%, and 51.0% for the switching cohort, add-on cohort, and naive cohorts, respectively. For the pre-index hypnotic drug, the proportion of BZDs was 23.0% in the switching cohort and 35.1% in the add-on cohort, while that of non-BZDs was 36.3% in the switching cohort and 47.3% in the add-on cohort. Regarding prescription history of the hypnotic drug, the

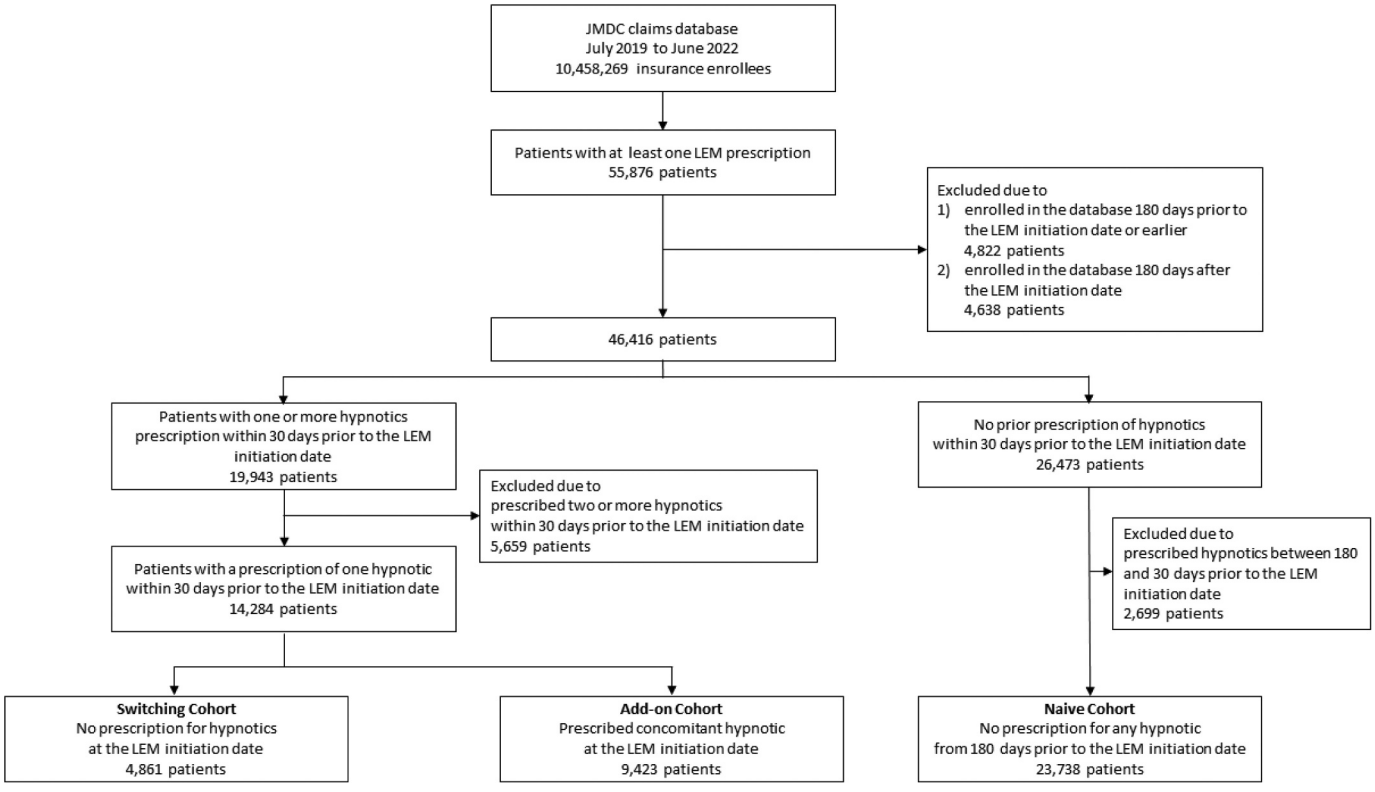

Figure 1. Flow diagram for the study cohorts of lemborexant initiators between 2019 and 2022 according to the other hypnotic drugs.

Abbreviation: LEM, lemborexant.

Table 1. Baseline and clinical characteristics.

		Switching cohort N = 4861		Add-on cohort N = 9423		Naive cohort N = 23,738	
Age (years), mean (SD)		41.8	14.7	43.8	13.7	40.6	14.2
Age group, n (%)	≤19 years	316	6.5%	352	3.7%	1393	5.9%
	20–29 years	857	17.6%	1308	13.9%	4774	20.1%
	30–39 years	877	18.0%	1720	18.3%	4749	20.0%
	40–49 years	1045	21.5%	2327	24.7%	5284	22.3%
	50–59 years	1182	24.3%	2504	26.6%	5219	22.0%
	≥60 years	520	10.7%	1039	11.0%	1983	8.4%
Male, n (%)		2352	48.4%	4695	49.8%	12118	51.0%
Comorbidities, n (%)†	Depression	3176	65.3%	5945	63.1%	12287	51.8%
	Schizophrenia spectrum disorders	1014	20.9%	2005	21.3%	2409	10.1%
	Hypertension	927	19.1%	1887	20.0%	3884	16.4%
	Diabetes	565	11.6%	1194	12.7%	2354	9.9%
	Chronic liver disease	555	11.4%	1155	12.3%	2154	9.1%
	Asthma	540	11.1%	1023	10.9%	2015	8.5%
	Obstructive sleep apnea syndrome	5	0.1%	19	0.2%	56	0.2%
	Charlson Comorbidity Index						
	0	3644	75.4%	7098	75.3%	19135	80.6%
	1–2	944	19.4%	1792	19.0%	3784	15.9%
	≥3	253	5.2%	533	5.7%	819	3.5%
Medication use, n (%)‡	Antidepressants	2151	44.2%	4010	42.5%	7945	33.4%
	Anxiolytics	1386	28.5%	3121	33.1%	6355	26.7%
	Antipsychotics	1411	29.0%	2602	27.6%	4579	19.2%
	Analgesics	1176	24.2%	2272	24.1%	4854	20.4%
	Antihypertensive drugs	809	16.6%	1618	17.2%	3400	14.3%
	Antiepileptic drugs	586	12.1%	1152	12.2%	1519	6.4%
	Opioids	174	3.6%	292	3.1%	607	2.6%
Pre-index hypnotic use, n (%)							
Prescription period†	0–<30 days	931	19.2%	1721	18.2%	–	–
	30–<180 days	1131	23.2%	1166	12.4%	–	–
	≥180 days	2799	57.6%	6536	69.4%	–	–
Pre-index hypnotic class‡	BZD	1116	23.0%	3312	35.1%	–	–
	Non-BZD	1765	36.3%	4455	47.3%	–	–
	MRA	511	10.5%	890	9.4%	–	–
	DORA	1469	30.2%	766	8.1%	–	–

Abbreviation: BZD, Benzodiazepines; DORA; Dual orexin receptor antagonists; Non-BZD, Non-benzodiazepines; MRA, Melatonin receptor agonists; SD, standard deviation.
†Measured for 180 days before the index date (Days [−180, −1]).
‡Measured for 30 days before the index date (Days [−30, −1]).

proportion with ≥180 days was 57.6% in the switching cohort and 69.4% in the add-on cohort. The other baseline and clinical characteristics were well balanced across the cohorts. The description of baseline characteristics by subgroup with the hypnotic class is shown in Supplementary materials 3. The overall trend was not different from those of the overall cohort.

3.2. Prescription patterns of LEM

Table 2 describes the prescription pattern of LEM. The mean ± SD of the initial dose of LEM were 4.74 ± 1.45, 4.60 ± 1.36, and 4.43 ± 1.21 for the switching cohort, add-on, cohort, and naive cohort, respectively. The usual starting dose of LEM in the package insert is 5 mg, but the initial LEM dose was mainly less than 5 mg for all

Table 2. Prescription pattern of lemborexant (LEM).

	Switching cohort N = 4861		Add-on cohort N = 9423		Naive cohort N = 23,738	
Initial dose (mg/day), mean (SD)	4.74	(1.45)	4.60	(1.36)	4.43	(1.21)
Initial dose pattern, n (%)						
≤2.5 mg	907	18.7%	2019	21.4%	5862	24.7%
2.5 mg<-5 mg	3757	77.3%	7148	75.9%	17636	74.3%
5 mg<-10 mg	197	4.1%	256	2.7%	240	1.0%
Number of prescribed days of LEM (days), median [IQR]	64	[21, 180]	57	[15, 180]	29	[15, 87]
Number of patients who continued prescription of LEM, n (%)						
at Day 30	3247	66.8%	5991	63.6%	11343	47.8%
at Day 90	2134	43.9%	3927	41.7%	5839	24.6%
at Day 180	1545	31.8%	2843	30.2%	3522	14.8%
Pre-index hypnotic use between Day −30 and Day −1						
Potency, mean (SD) †	0.56	(0.39)	0.67	(0.61)	–	–
Regular use with potency, n (%)‡	1350	27.8%	3969	42.1%	–	–
As-needed use with potency, n (%)‡	3511	72.2%	5454	57.9%	–	–

Abbreviations: IQR, interquartile range; LEM, lemborexant; SD, standard deviation.
†Potency was defined as a value calculated by multiplying the flunitrazepam-equivalent dose and number of days for 30 days divided by 30.
‡Regular use was defined by potency > 0.8, and as-needed use was defined by potency ≤ 0.8.

cohorts. The initial LEM dose in the naive cohort was lower than in the other two cohorts, and the initial LEM dose in the switching and add-on cohorts showed a similar tendency. The median number of prescribed days was 29 days in the naive cohort, which was also lower than the 64 days in the switching cohort and 57 days in the add-on cohort. Although there were no marked differences in the LEM prescription pattern between the switching and add-on cohort, there was a different trend in the potency and class of pre-index hypnotics: potency and the proportion of regular use of pre-index hypnotics showed relatively higher values in the add-on cohort (42.1%) than in the switching cohort (27.8%).

3.3. Proportion of successful switching during the follow-up period

Table 3 shows the proportion of successful switching to LEM stratified by the three cohorts. For the switching cohort, the success proportion at Day 180 was 70.1%, broken down into no hypnotic and LEM monotherapy treatment proportions of 41.9% and 28.2%, respectively. For the add-on cohort, the success proportion at Day 180 was 38.6%, broken down into no hypnotic and LEM monotherapy treatment proportions of 26.6% and 12.0%, respectively. The success proportion at Day 180 for the naive cohort was 86.6%. To summarize the results, the proportion of successful switching in the switching cohort was slightly lower, and that in the add-on cohort was considerably lower than in the naive cohort. Approximately two-thirds of successfully switching patients had discontinued both LEM and other hypnotics at Day 180.

Table 4 shows a subgroup analysis of the success proportions at Day 180. In the add-on cohort, the success proportions with the previously prescribed duration of hypnotics of <30 days, 30-<180 days, and ≥180 days were 61.4%, 44.9%, and 31.4%, respectively. Additionally, the success proportions in patients with pre-prescribed BZDs and non-BZDs were 31.5% and 37.6%, while proportions in those with MRA and DORA were 50.1% and 61.0%, or in other words relatively higher than those with BZDs or non-BZDs. Regarding the subgroups by potency of prescribed hypnotics before Day 0, the success proportion of regular use was 25.8%, and that of as-needed use was 47.8%. These results in the add-on cohort showed that the proportion of successful switching was lower in patients with long-term hypnotic use, higher potency, or prescription of BZDs or non-BZDs. Although success

Table 3. Analytical results for the proportion of successful switching at day 180.

	Switching cohort $N = 4861$		Add-on cohort $N = 9423$		Naive cohort $N = 23{,}738$	
Evaluation of switching at follow-up period	n	%	n	%	n	%
Success of switching to LEM	3407	70.1%	3633	38.6%	20555	86.6%
No prescription of LEM or other hypnotics	2035	41.9%	2505	26.6%	17424	73.4%
Prescription of LEM alone	1372	28.2%	1128	12.0%	3131	13.2%
Failure of switching to LEM	1454	29.9%	5790	61.4%	3183	13.4%

Abbreviations: LEM, lemborexant.

Table 4. Subgroup analysis: results for the proportion of successful switching at day 180.

		Switching cohort			Add-on cohort			Naive cohort		
		Total	Successful switched patients		Total	Successful switched patients		Total	Successful switched patients	
		N	n	%	N	n	%	N	n	%
Age	≦ 19 years	316	252	79.7%	352	171	48.6%	1393	1199	86.1%
	20-29 years	857	608	70.9%	1308	613	46.9%	4774	4048	84.8%
	30-39 years	877	629	71.7%	1720	676	39.3%	4749	4032	84.9%
	40-49 years	1045	725	69.4%	2327	857	36.8%	5284	4581	86.7%
	50-59 years	1182	794	67.2%	2504	853	34.1%	5219	4597	88.1%
	≥60 years	520	357	68.7%	1039	408	39.3%	1983	1791	90.3%
Sex	Male	2352	1664	70.7%	4695	1843	39.3%	12118	10488	86.5%
	Female	2509	1743	69.5%	4728	1790	37.9%	11620	10067	86.6%
Prescription duration of hypnotics prior to index date †	0-<30 days	931	701	75.3%	1721	1056	61.4%			
	30-<180 days	1131	803	71.0%	1166	523	44.9%			
	≥180 days	2799	1903	68.0%	6536	2054	31.4%			
Pre-index hypnotics ‡	BZD	1116	708	63.4%	3312	1043	31.5%			
	Non-BZD	1765	1156	65.5%	4455	1677	37.6%			
	MRA	511	404	79.1%	890	446	50.1%			
	DORA	1469	1139	77.5%	766	467	61.0%			
Potency of pre-index hypnotics ‡, §	Regular use	1350	876	64.9%	3969	1024	25.8%			
	As needed use	3511	2531	72.1%	5454	2609	47.8%			
Pre-index antipsychotics ‡	Prescribed	1411	979	69.4%	2602	886	34.1%	4579	3892	85.0%
	None	3450	2428	70.4%	6821	2747	40.3%	19159	16663	87.0%
Pre-index antidepressants ‡	Prescribed	2151	1442	67.0%	4010	1379	34.4%	7945	6656	83.8%
	None	2710	1965	72.5%	5413	2254	41.6%	15793	13899	88.0%
Pre-index anxiolytics ‡	Prescribed	1386	928	67.0%	3121	1114	35.7%	6355	5376	84.6%
	None	3475	2479	71.3%	6302	2519	40.0%	17383	15179	87.3%

Abbreviation: BZD, Benzodiazepines; DORA; Dual orexin receptor antagonists; Non-BZD, Non-benzodiazepines; MRA, Melatonin receptor agonists.
†Measured for 180 days before the index date (Days [−180, −1]).
‡Measured for 30 days before the index date (Days [−30, −1]).
§Potency was defined as the value calculated by multiplying the flunitrazepam-equivalent dose and number of days for 30 days, divided by 30.

proportion was higher in the switching cohort than in the add-on cohort, tendencies among subgroups were similar in the two cohorts. The naive group had greater than 80% success proportions in all subgroups.

The results of logistic regression analysis show the association between background factors and success proportion, with odds ratios (ORs) greater than one indicating greater switching success, and the opposite for ORs less than one (Supplementary materials 4). Similar to the results from the subgroup analysis in Table 4, ORs were lower with a hypnotic history of ≥180 days, pre-prescribed with benzodiazepine or non-benzodiazepine, and higher potency with regular use.

The Sankey diagram shows a shift in prescribing patterns for Day 30, Day 90, and Day 180. In the switching cohort, 17.5% of patients had discontinued and 57.2% had switched to LEM monotherapy at Day 30. About half of those with LEM monotherapy at Day 30 moved to no hypnotics by Day 180, suggesting that a certain number of patients go through LEM monotherapy before moving to hypnotic discontinuation (Figure 2(a)). In the add-on cohort, sum of the success

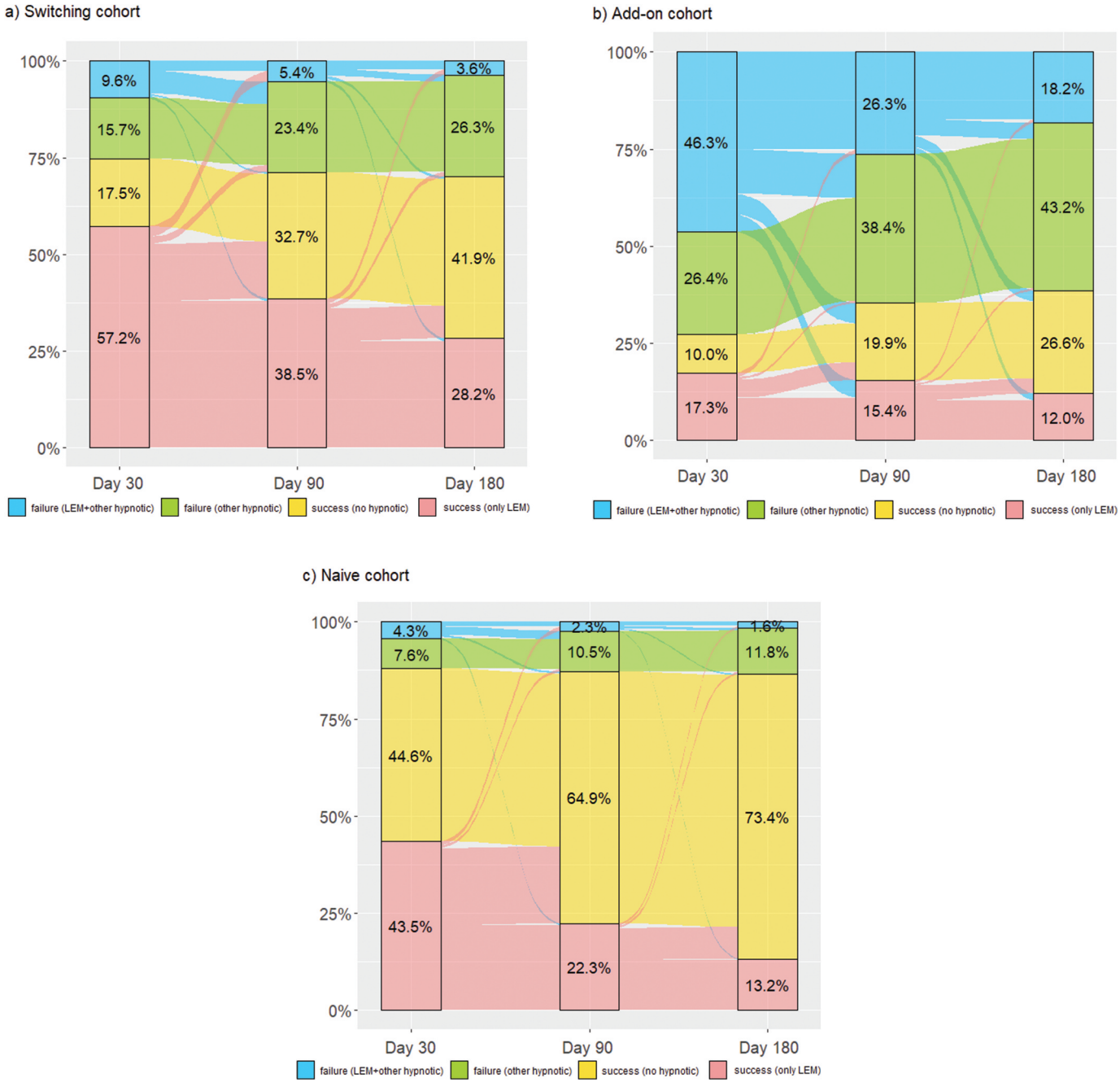

Figure 2. Sankey diagram for switching patterns of lemborexant and other hypnotics after lemborexant initiation. a) Switching cohort, b) Add-on cohort, c) Naive cohort.

Abbreviations: LEM, lemborexant

proportions at Day 30 was 27.3%, and increased to 38.6% on Day 180. These success proportions were lower than those of the switching cohort at all time points (Figure 2(b)). In the naive cohort, 88.1% of patients had switched to LEM monotherapy (43.5%) or no hypnotic (44.6%) at Day 30, and more than half of those with LEM monotherapy at Day 30 moved to no hypnotics by Day 180, as also seen in the switching cohort (Figure 2(c)).

3.4. Distribution of baseline and clinical factors between the failure group and the success group in the add-on cohort

Table 5 shows the distribution of baseline and clinical factors between the failure group and success group in the add-on cohort. The mean tapering period in the success group was 46.1 days. Although the mean ± SD (flunitrazepam-equivalent dose mg/day) of the total dose per day of hypnotics (including LEM) decreased from 1.37 ± 0.45 to 0.55 ± 0.24 in the success group, it remained unchanged from 1.51 ± 0.53 to 1.43 ± 0.68 in the failure group. In the failure group, the pre-index hypnotic dose was initially high, and no decrease was observed on Day 0 (mean: 1.01) or Day 180 (mean: 1.04). LEM dose increased slightly from Day 0 (mean: 0.50) to Day 180 (mean: 0.59). In contrast, in the success group, LEM dose remained unchanged, but the use of pre-index hypnotics was discontinued, following which all hypnotic doses decreased. This indicates that tapering of the dose of other hypnotics was not shown in the failure group. The proportion of prescriptions for psychotropics (antipsychotics, antidepressants, anxiolytics) was higher in the failure group than in the success group at both Day 0 and Day 180, and prescription history tended to be longer. In the success group, the proportion of as-needed use was higher than in the failure group (71.8% and 49.1%, respectively). Consistent with this, the proportion of prescription duration of hypnotics before Day 0 with less than 30 days was higher than in the failure group (29.1% and 11.5%, respectively).

4. Discussion

This study is the first to investigate the actual state of switching to and add-on of LEM using a large-scale nationwide claims database. Among patients who were prescribed a single hypnotic drug and prescribed LEM initially, 34% (= 4861/14284) of patients stopped taking the existing hypnotic drug when starting LEM (switching cohort), while 66% (= 9423/14284) of patients added LEM in combination of the existing hypnotic drug (add-on cohort). In both cohorts, the most common hypnotic drugs prescribed before the start of LEM were non-BZDs and BZDs. For the follow-up period of 6 months after starting LEM, 70.1% of patients in the switching cohort had successfully switched, as had 38.6% of patients in the add-on cohort. Furthermore, in the add-on cohort, the potency of the previously prescribed hypnotic drug before the start of LEM in the failure group was higher than in the success group; moreover, dose of the other hypnotics did not decrease for 6 months after the start of LEM in the failure group.

Table 5. Distributions of baseline and clinical factors between the failure group and success group in add-on cohort patients.

		Success group $N = 3633$			Failure group $N = 5790$		
Clinical factors		N	mean	SD	N	mean	SD
Tapering period of hypnotics (days), mean (SD)		3633	46.1	54.3	–	–	–
Total duration of LEM prescription (days), mean (SD)		3633	144.7	150.4	5790	128.1	160.2
Flunitrazepam-equivalent dose per day†, mean (SD)							
Overall hypnotics (LEM + the other hypnotics)	at Day 0	3633	1.37	0.45	5790	1.51	0.53
	at Day180‡	1000	0.55	0.24	1592	1.43	0.68
Other hypnotics	at Day 0	3633	0.87	0.38	5790	1.01	0.48
	at Day180‡	0	–	–	1326	1.04	0.53
LEM	at Day 0	3633	0.50	0.19	5790	0.50	0.20
	at Day180‡	1000	0.55	0.24	1517	0.59	0.26
		N	n	%	N	n	%
Prescription of antipsychotics, n (%)	at Day 0	3633	1341	36.9%	5790	1716	29.6%
	at Day180‡	1123	298	26.5%	1715	683	39.8%
Prescription of antidepressants, n (%)	at Day0	3633	1379	37.9%	5790	2631	45.4%
	at Day180‡	1123	527	46.9%	1715	897	52.3%
Prescription of anxiolytics, n (%)	at Day0	3633	1114	30.3%	5790	2007	34.6%
	at Day180‡	1123	293	26.0%	1715	567	33.0%
Class of the hypnotic drug at pre-index period, n (%)	BZD	3633	1043	28.7%	5790	2269	39.2%
	Non-BZD	3633	1677	46.2%	5790	2778	48.0%
	MRA	3633	446	12.3%	5790	444	7.7%
	DORA	3633	467	12.9%	5790	299	5.2%
Potency of the hypnotic drug at pre-index period, n (%)	As-needed use	3633	2609	71.8%	5790	2845	49.1%
	Regular use	3633	1024	28.2%	5790	2945	50.9%
Prescription duration of hypnotics prior to Day 0, n (%)	0-<30 days	3633	1056	29.1%	5790	665	11.5%
	30-<180 days	3633	523	14.4%	5790	643	11.1%
	≥180 days	3633	2054	56.5%	5790	4482	77.4%

Abbreviation: BZD, Benzodiazepines; DORA; Dual orexin receptor antagonists; LEM, lemborexant; Non-BZD, Non-benzodiazepines; MRA, Melatonin receptor agonists; SD, standard deviation.

†Daily doses of all hypnotics were transformed by flunitrazepam-equivalent conversion.

‡Patients without a prescription for any hypnotic, including LEM, on Day 180 were excluded from this row (at Day 180).

Successful switching was evaluated as LEM alone or no hypnotic at 6 months after starting LEM separately. In the switching cohort, the overall success proportion was 70.1%, of which 28.2% continued LEM alone and 41.9% discontinued all hypnotics (Table 3). The success proportion of the switching cohort was relatively close to that of the naive cohort. This result indicates that the therapeutic strategy based on starting LEM while discontinuing the existing hypnotic is being used clinically to attempt to induce discontinuation of all hypnotics [4,25].

In contrast, the success proportion in the add-on cohort was low, at 38.6% (Table 3). Table 1 shows a tendency for more patients in the add-on cohort than in the switching cohort to have a long history of prescription of hypnotics, to use BZDs or non-BZDs, and to experience a high potency of hypnotics. Furthermore, Table 4 shows that the success proportion tended to be low in patients having a long history of hypnotics, use of BZDs or non-BZDs, and high potency. The previous research showed that patients treated continuously for less than 8 months with sedative-benzodiazepines had an incidence of withdrawal of 5%, whereas 43% of patients treated for 8 months or more demonstrated clear withdrawal reactions [26]. The findings in our study are consistent with previous reports that BZDs and non-BZDs are highly addictive and that it is difficult to switch to other treatments or to reduce or stop taking them [26,27]. The higher proportion of BZDs and non-BZDs may suggest that the higher baseline severity of insomnia in the add-on cohort has prevented the transition to LEM monotherapy and discontinuation of hypnotics. Since long-term BZD or non-BZD prescription is a safety concern [26–29], a treatment strategy to switch to LEM earlier may be considered in discussion with the patient during insomnia treatment.

Subgroup analysis of clinical and baseline factors between the success and failure groups in the add-on cohort (Table 5) showed that the tapering of pre-index hypnotics was not achieved in the failure group. This may have been related to the failure of tapering or discontinuing the hypnotics. Previous studies reported that patients prescribed higher doses of BZDs or longer administration of BZDs before switching to LEM tended to fail tapering or discontinuation of BZDs [16,18], and similar trends were confirmed in our present study.

According to expert consensus on insomnia treatment in Japan, if the effect of BZDs is insufficient with drug therapy, the recommended order is switching to LEM, combination therapy with LEM, switching to suvorexant, and combination therapy with suvorexant [4]. One previous study reported that scores on the Athens Insomnia Scale improved significantly in patients who switched from BZDs to LEM [17], suggesting an improvement in insomnia severity. This may be the reason why the switching cohort in our present study showed a high switching success proportion. Furthermore, that study also found that patients who switched to LEM had a shorter duration of insomnia, a lower BZD dose, and a shorter treatment period than those who continued BZDs [16]. Therefore, it is possible that patients with severe insomnia and related comorbidities may be more likely to change their hypnotic treatment pattern by adding LEM to treated hypnotics rather than discontinuing hypnotics for switching to LEM.

In the switching cohort, the proportion of switching from the DORA (suvorexant) was 30.2%, which was higher than in the add-on group (8.1%) (Table 1). The results of a network meta-analysis also revealed that LEM showed improvement in subjective time to sleep onset (sTSO), subjective total sleep time (sTST) and subjective wake after sleep onset (sWASO) compared to suvorexant [30,31]. The reason for this high proportion is that switching between DORAs is highly safe with few side effects [32]. Furthermore, it has been reported that sleep onset difficulties were significantly improved when switching from suvorexant to LEM [32]. These results suggest that patients switched to LEM with the hope of improving sleep onset problems and insomnia severity.

Table 3 shows that the naive cohort set up as a control had 86.6% of patients on LEM alone or without any hypnotic at Day 180. Figure 2 shows the prescription pattern on Day 30, Day 90, and Day 180. The proportion of LEM monotherapy prescriptions in the naive cohort at Day 30 was 43.5%, versus 57.2% in the switching cohort and a low 17.3% in the add-on cohort. In addition, the proportion of patients who discontinued all hypnotics (including LEM) in the naive cohort at Day 30 was 44.6%, versus 17.5% in the switching cohort and 10.0% in the add-on cohort. These results are similar to a previous report which showed that approximately 60% of patients who were prescribed hypnotics for the first time discontinued the prescription after only 1 month [33]. One explanation for the high proportion of discontinuation of all hypnotics in the naive cohort was that there were fewer patients with comorbidities, and many patients did not receive insomnia treatment for a long period.

Several limitations of our study warrant mention. First, we defined the discontinuation of LEM as no prescription for 31 days or more after the end date of the previous prescription. Accordingly, successful switching in this study did not consider recurrent insomnia within 31 days after the end of the LEM prescription period. However, it is not possible to determine from the claims database whether the patient's insomnia had remitted after discontinuation of the LEM and the severity of insomnia at baseline is also unknown, so verification through future research is required. Second, this study considered switching to another hypnotic drug at Day 180 or at the end of the LEM prescription period. In actual clinical practice, however, switching from LEM to psychotropics other than hypnotics may be considered, and this possibility was not considered in this study. Third, the previous study has reported an increase in prevalence of insomnia from the age of 50 years and above [3] and these patients were included in the present study. However, elderly patients aged ≥65 years, who account for a large proportion of prevalent patients with insomnia, were not included in this study. Therefore, the actual status of switching pattern of hypnotics in the elderly patients is a future issue. Fourth, the add-on cohort in this study was defined as patients in whom the prescription period of the pretreatment hypnotic overlapped with Day 0. When switching from a pretreatment hypnotic to LEM, it is also possible that the pretreatment drug may be discontinued after a short period of concomitant use, but this study did not consider these conditions. However, it is possible that there were many patients in the success group who

completed the previous treatment within a short period of time. Fifth, in the add-on cohort, some patients may have originally had difficult-to-treat refractory cases of insomnia. These patients might not have had the opportunity to switch. Further research that takes account of patient characteristics is necessary to solve this question. Sixth, our research does not consider over-the-counter drugs or medical expenses not covered by insurance. However, the effectiveness of these drugs might be considered mild, and we consider that they likely had no significant impact on the results of the present study. Lastly, analysis of prescription patterns coincided with the Coronavirus disease 2019 (COVID-19) pandemic period. The impact of hypnotic treatment during the COVID-19 pandemic period has been inconsistent, with some reporting an increase in sleep disorders [34] and others a possible decrease in outpatient visits. Therefore, it may be necessary to evaluate the generalizability of the present study with data from the post-COVID-19 pandemic period.

5. Conclusion

This study investigated the treatment patterns of switching from other hypnotics to LEM using a large-scale claims database. In the switching cohort, 70.1% of patients had successfully switched at 6 months after LEM initiation, close to 86.6% in the naive cohort, while 38.6% switched successfully in the add-on cohort. The success proportion tended to be lower in patients who had a long history of treatment with hypnotics, had a high prescription dose of hypnotics, or were using BZDs or non-BZDs. The lower success proportion in the add-on cohort might be related to clinically more severe insomnia or a concomitant prescription of BZDs or non-BZDs, from which discontinuation may be challenging. Since long-term BZD or non-BZD prescription is a safety concern, a treatment strategy to switch to LEM earlier may be considered in discussion with the patient during insomnia treatment. Further research that takes account of patient characteristics is also necessary.

Data availability statement

Data is not available due to ethical restrictions.

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Author contributions

S Tanaka-Mizuno contributed to the study design, data analysis, and writing of the manuscript. K Fujimoto, Y Sakata, M Ishii, T Taninaga, N Kubota, and M Moline contributed to study design, data collection, and writing of the manuscript. T Fukasawa, K Mizuno, S Yoshida, and K Kawakami were involved in study design, data analysis, and contributed to study design and writing of the manuscript. K Mishima contributed to study design and interpretation of the medical aspects of the study. All authors contributed to the interpretation of the data and review of the manuscript and approved this manuscript for submission.

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ORCID

Sachiko Tanaka-Mizuno http://orcid.org/0000-0003-0671-5376

References

1. Roth T, Coulouvrat C, Hajak G, et al. Prevalence and perceived health associated with insomnia based on DSM-IV-TR; international statistical classification of diseases and related health problems, tenth Revision; and research diagnostic criteria/international classification of sleep disorders, second edition criteria: results from the America Insomnia Survey. Biol Psychiatry. 2011;69(6):592–600. doi: 10.1016/j.biopsych.2010.10.023
2. Chiba T, Hagiwara Y, Hifumi T, et al. Prevalence and risk factors of insomnia and sleep-aid use in emergency physicians in Japan: secondary analysis of a nationwide survey. West J Emerg Med. 2023;24(2):331–339. doi: 10.5811/westjem.2022.12.57910
3. Itani O, Kaneita Y, Munezawa T, et al. Nationwide epidemiological study of insomnia in Japan. Sleep Med. 2016;25:130–138. doi: 10.1016/j.sleep.2016.05.013
4. Takaesu Y, Sakurai H, Aoki Y, et al. Treatment strategy for insomnia disorder: Japanese expert consensus. Front Psychiatry. 2023;14:1168100. doi: 10.3389/fpsyt.2023.1168100
5. Inada K, Enomoto M, Yamato K, et al. Prescribing pattern of hypnotic medications in patients initiating treatment at Japanese hospitals: a nationwide, retrospective, longitudinal, observational study using a claims database. Drugs Real World Outcomes. 2021;8(3):277–288. doi: 10.1007/s40801-021-00244-9
6. Schroeck JL, Ford J, Conway EL, et al. Review of safety and efficacy of sleep medicines in older adults. Clin Ther. 2016;38(11):2340–2372. doi: 10.1016/j.clinthera.2016.09.010
7. Bertisch SM, Herzig SJ, Winkelman JW, et al. National use of prescription medications for insomnia: NHANES 1999–2010. Sleep. 2014;37(2):343–349. doi: 10.5665/sleep.3410
8. Davies SJ, Rudoler D, de Oliveira C, et al. Comparative safety of chronic versus intermittent benzodiazepine prescribing in older adults: a population-based cohort study. J Psychopharmacol. 2022;36(4):460–469. doi: 10.1177/02698811211069096

9. Scharner V, Hasieber L, Sönnichsen A, et al. Efficacy and safety of Z-substances in the management of insomnia in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing. BMC Geriatr. 2022;22(1):87. doi: 10.1186/s12877-022-02757-6
10. Khan H, Garg A, Yasmeen, et al. Zolpidem use and risk of suicide: a systematic review and meta-analysis. Psychiatry Res. 2022;316:114777. doi: 10.1016/j.psychres.2022.114777
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition (DSM-V). Washington (DC): American Psychiatric Association; 2013. doi: 10.1176/appi.books.9780890425596
12. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien (IL): American Academy of Sleep Medicine; 2014.
13. De Crescenzo F, D'Alò GL, Ostinelli EG, et al. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. Lancet. 2022;400:170–184. doi: 10.1016/S0140-6736(22)00878-9
14. McElroy H, O'Leary B, Adena M, et al. Comparative efficacy of lemborexant and other insomnia treatments: a network meta-analysis. J Manag Care Spec Pharm. 2021;27(9):1296–1308. doi: 10.18553/jmcp.2021.21011
15. Ikeda S, Azuma MK, Fujimoto K, et al. Cost-effectiveness analysis of lemborexant for treating insomnia in Japan: a model-based projection, incorporating the risk of falls, motor vehicle collisions, and workplace accidents. Psychol Med. 2022;52(13):2822–2834. doi: 10.1017/S0033291722000356
16. Suzuki H, Hibino H. Characteristics of patients who were able to switch from benzodiazepine hypnotics to lemborexant. SAGE Open Med. 2021;9:20503121211037904. doi: 10.1177/20503121211037903
17. Katsuta N, Takahashi K, Kurosawa Y, et al. Safety and real-world efficacy of lemborexant in the treatment of comorbid insomnia. Sleep Med X. 2023;5:100070. doi: 10.1016/j.sleepx.2023.100070
18. Usui K, Fujii Y, Okada K, et al. Low dose benzodiazepine receptor agonists may be completely replaced by lemborexant at about the same dose. PCN Rep. 2022;1(3):1. doi: 10.1002/pcn5.32
19. Fukasawa K, Sekimoto T, Kaneko K, et al. Effects of sleeping medication switching on falls and the risk assessment according to functional mechanism in chronic hospitals. Jpn J Pharm Health Care Sci. 2020;46:323–330. doi: 10.5649/jjphcs.46.323
20. Nagai K, Tanaka T, Kodaira N, et al. Data resource profile: JMDC claims database sourced from health insurance societies. J Gen Fam Med. 2021;22(3):118–127. doi: 10.1002/jgf2.422
21. Yoshida S, Takeuchi M, Tanaka-Mizuno S, et al. Clinical epidemiology and pharmacoepidemiology studies with real-world databases. Proc Jpn Acad Ser B Phys Biol Sci. 2022;98:517–528. doi: 10.2183/pjab.98.026
22. Nakahata M, Tanaka-Mizuno S, Yamaguchi F, et al. Does nutritional guidance reduce cardiovascular events in patients with type 2 diabetes mellitus? A retrospective cohort study using a nationwide claims database. Acta Diabetol. 2023;60(11):1541–1549. doi: 10.1007/s00592-023-02147-3
23. Yamamoto-Sasaki M, Yoshida S, Takeuchi M, et al. Association between antidepressant use during pregnancy and congenital anomalies in children: a retrospective cohort study based on Japanese claims data. Congenit Anom. 2020;60(6):180–188. doi: 10.1111/cga.12386
24. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676–682. doi: 10.1093/aje/kwq433
25. Horikoshi S, Miura I, Suzuki Y, et al. Switching to lemborexant for the management of insomnia in mental disorders: the SLIM study. J Clin Sleep Med. 2023;19(10):1753–1758. doi: 10.5664/jcsm.10668
26. Rickels K, Case WG, Downing RW, et al. Long-term diazepam therapy and clinical outcome. JAMA. 1983;250(6):767–771. doi: 10.1001/jama.1983.03340060045024
27. Petursson H, Lader MH. Benzodiazepine dependence. Br J Addict. 1981;76(2):133–145. doi: 10.1111/j.1360-0443.1981.tb00218.x
28. Gorgels WJMJ, Oude Voshaar RC, Mol AJJ, et al. Predictors of discontinuation of benzodiazepine prescription after sending a letter to long-term benzodiazepine users in family practice. Fam Pract. 2006;23(1):65–72. doi: 10.1093/fampra/cmi065
29. Mokhar A, Kuhn S, Topp J, et al. Long-term use of benzodiazepines and Z drugs: a qualitative study of patients' and healthcare professionals' perceptions and possible levers for change. BJGP Open. 2019;3(1):bjgpopen18X101626. doi: 10.3399/bjgpopen18X101626
30. Kishi T, Nomura I, Matsuda Y, et al. Lemborexant vs suvorexant for insomnia: a systematic review and network meta-analysis. J Psychiatr Res. 2020;128:68–74. doi: 10.1016/j.jpsychires.2020.05.025
31. Ozone M, Hirota S, Ariyoshi Y, et al. Efficacy and safety of transitioning to lemborexant from Z-drug, suvorexant, and ramelteon in Japanese insomnia patients: an open-label, multicenter study. Adv Ther. 2024;41(4):1728–1745. doi: 10.1007/s12325-024-02811-2
32. Okino K, Suzuki H, Kondo S, et al. Effectiveness of change from suvorexant to lemborexant drug in the treatment of sleep disorders. Psychogeriatrics. 2022;22(5):595–604. doi: 10.1111/psyg.12858
33. Enomoto M, Kitamura S, Tachimori H, et al. Long-term use of hypnotics: analysis of trends and risk factors. Gen Hosp Psychiatry. 2020;62:49–55. doi: 10.1016/j.genhosppsych.2019.11.008
34. Partinen M, Holzinger B, Morin CM, et al. Sleep and daytime problems during the COVID-19 pandemic and effects of coronavirus infection, confinement and financial suffering: a multinational survey using a harmonised questionnaire. BMJ Open. 2021;11(12):e050672. doi: 10.1136/bmjopen-2021-050672