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ORIGINAL RESEARCH ARTICLE

Factors Associated with Prescriptions for an Orexin Receptor Antagonist Among Japanese Patients with Insomnia: Analysis of a Nationwide Japanese Claims Database

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Abstract

Background Few studies have examined the prescribing patterns of orexin receptor antagonists (ORAs) in the real-world clinical setting in Japan.

Objective We sought to analyze the factors associated with ORA prescriptions for patients with insomnia in Japan.

Methods Outpatients (aged ≥ 20 to < 75 years old) prescribed one or more hypnotic for insomnia between April 1, 2018 and March 31, 2020 with continuous enrollment for ≥ 12 months were extracted from the JMDC Claims Database. We performed multivariable logistic regression to identify factors (patient demographics and psychiatric comorbidities) associated with ORA prescription in new or non-new users of hypnotics (patients without or with hypnotics prescription history, respectively).

Results Of 58,907 new users, 11,589 (19.7%) were prescribed ORA at the index date. Male sex (odds ratio [OR] 1.17, 95% confidence interval [CI] 1.12–1.22) and presence of bipolar disorders (OR 1.36, 95% CI 1.20–1.55) were associated with greater odds of ORA prescription. Among 88,611 non-new users, 15,504 (17.5%) were prescribed ORA at the index date. Younger age and several psychiatric comorbidities, such as neurocognitive disorders (OR 1.64, 95% CI 1.15–2.35), substance use disorders (OR 1.19, 95% CI 1.05–1.35), bipolar disorders (OR 1.14, 95% CI 1.07–1.22), schizophrenia spectrum disorders (OR 1.07, 95% CI 1.01–1.14), and anxiety disorders (OR 1.05, 95% CI 1.00–1.10), were associated with greater odds of ORA prescription.

Conclusion This is the first study to determine the factors associated with ORA prescriptions in Japan. Our findings could help guide appropriate insomnia treatment using ORAs.

1 Background

Insomnia is a serious condition which is characterized by disordered sleep duration, poor sleep quality, and difficulty initiating or maintaining sleep [1]. It may have significant effects on daytime functioning and overall quality of life, which may persist for many years. Insomnia thus imposes an immense burden not only on the affected individual but also to broader society [1]. Furthermore, accumulating evidence suggests that the ongoing COVID-19 pandemic may impact on sleep. Insomnia is observed in patients during and after COVID-19 infection [2]. Insomnia was also reported to be the most common mental health problem among healthcare workers during the COVID-19 pandemic [3].

Although the underlying pathophysiology of insomnia remains poorly understood, the treatment options have involved non-pharmacological therapy, such as cognitive behavioral therapy (CBTi), and/or pharmacological therapy with hypnotics. However, in Japan, CBTi has not yet been covered by health insurance, thus application of CBTi is limited. Currently, pharmacological therapy with hypnotics has been the predominant treatment option in Japan [4–7] and according to the Japanese Society of Sleep Research guidelines, CBTi is positioned as a second-line treatment for patients who do not respond adequately to pharmacotherapy [8].

Better understanding of the pathophysiology of insomnia has led to the development and introduction of several novel classes of drugs, including the melatonin receptor agonist ramelteon approved in 2010 and the orexin receptor

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Key Points

To date, few studies have examined the prescribing patterns of orexin receptor antagonists (ORAs) in the real-world clinical setting in Japan.

We performed analyses of the JMDC Claims Database to obtain insight into the prescribing practices for an ORA among new and non-new users of hypnotics in Japan. Factors associated with ORA prescription included patient demographics (age, sex, medical specialty, clinical setting) and presence of psychiatric comorbidities.

These findings provide insight into the clinical factors that may be considered by physicians when prescribing ORA in Japan. This information could be useful in informing the appropriate use of ORAs for treating insomnia.

antagonist (ORA) suvorexant approved in 2014 (followed by lemborexant in July 2020) in Japan [9–11]. We previously examined the changes in the treatment landscape for insomnia for the period between April 2010 and March 2020 [12]. Analysis of prescription trends among new users of sleep medications showed that over 90% of insomnia patients were prescribed $GABA_A$ receptor agonists (benzodiazepines [BZD] or non-benzodiazepines [z-drugs]) in the fiscal year 2010. While the percentage of patients prescribed BZD decreased over time, the percentage of those prescribed an ORA (suvorexant in this study) increased, with approximately 20% of patients being newly prescribed an ORA in the fiscal year 2019.

Further research to examine the prescribing practices for ORA would help clarify how clinicians prescribe this drug in real-world clinical practice. In fact, some reports of post-marketing surveillance have revealed that suvorexant is prescribed to insomnia patients across broad demographic and clinical backgrounds, including patients with psychiatric disorders or dementia [13]. In addition, evidence regarding the efficacy and safety profiles of suvorexant in insomnia patients with various comorbidities is steadily accumulating [14–16]. However, few studies have examined ORA prescription patterns in the real-world clinical setting in Japan. Therefore, we extended the analyses reported in our previous study [12] to analyze which factors are associated with ORA prescriptions in patients with insomnia in Japan. In this study, we focused on two cohorts of patients—new users and non-new users of hypnotics—because our previous study [12] revealed some differences in the prescription patterns for hypnotics between these patient groups. We anticipated that the clinical and demographic factors associated with the prescription of hypnotics would differ between new and non-new users.

2 Methods

2.1 Data Source

As we reported previously [12], we used the JMDC Claims Database [17] as the data source for this retrospective study (study period: April 1, 2017 to March 31, 2020). The JMDC Claims Database is the largest health insurance claims database in Japan. It collects claims data for individuals who belong to health insurance providers for company employees and their families as part of the Japanese union-managed health insurance system. All data are anonymized to prevent identification of individual patients. Patients registered in the JMDC Claims Database can be followed up despite a change in their treating facility, unlike records from individual institutions where patients may be lost to follow-up. In the database, diagnoses and drug records are standardized and mapped to International Classification of Diseases, 10th Edition (ICD-10) codes and Anatomical Therapeutic Chemical (ATC) codes, respectively.

2.2 Patients

For the purpose of this study, we extracted data for patients satisfying the following criteria: aged ≥ 20 to < 75 years old, diagnosis of insomnia (ICD-10 code G470), prescription for one or more hypnotic between April 1, 2018 and March 31, 2020 (index period), and continuous enrollment for ≥ 12 months before the index date (Fig. 1). In the present study, we only analyzed data for outpatients. The index date was defined as the date of the first recorded prescription of one or more hypnotic during the index period. For patients with a recorded prescription in this period, we extracted their hypnotics prescription data for a 12-month pre-index period to identify their prescription history of hypnotics. Patients were excluded for the following reasons: one or more diagnosis of narcolepsy and/or cataplexy (G474) during the study period, hospitalization at the index date, missing data for the hypnotics prescription date during the study period, or use of hypnotics lacking prescription information during the study period. We excluded patients with narcolepsy and/or cataplexy in the present study because ORA (suvorexant) should be administered with caution in patients with narcolepsy or catalepsy in Japan in accordance with the package insert [18]. When identifying factors associated with its prescription, we considered that such items should be excluded from the analysis. Hospitalized patients were excluded because we wished to focus on outpatient use of hypnotics and because the data for inpatients lacked information on whether hypnotics were prescribed for

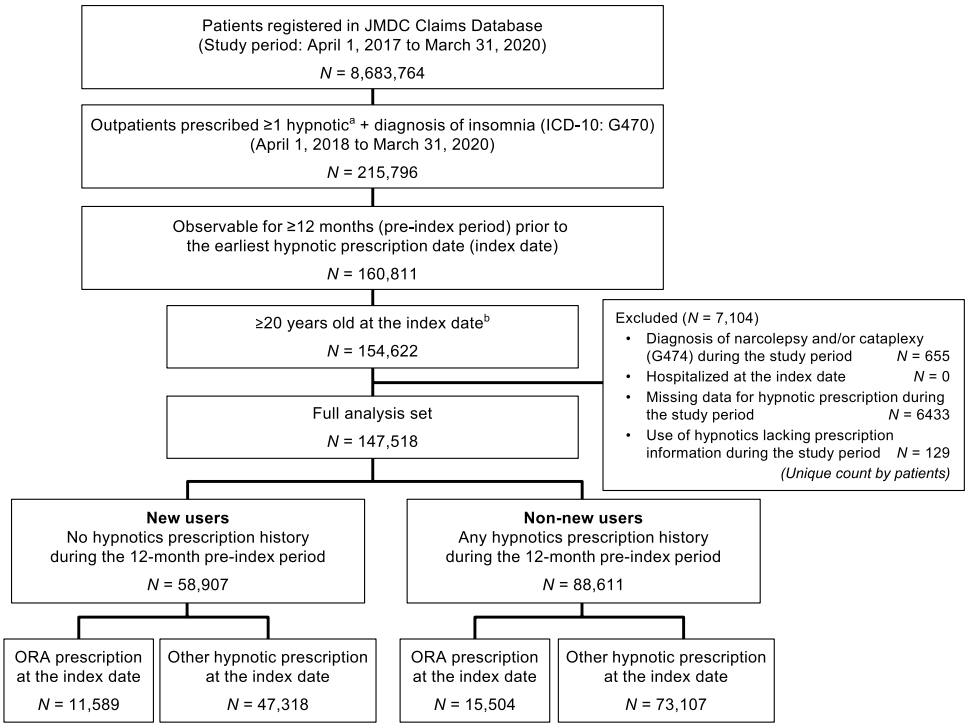

Fig. 1 Patient disposition. *ICD-10* International Classification of Diseases, 10th Edition, *ORA* orexin receptor antagonist. [a]Patients who were prescribed hypnotics as *pro re nata* only at the index date and patients with overlapping prescriptions for hypnotics from two or more physicians at the index date were excluded at the enrollment phase. [b]Patients aged ≥ 75 years are not included in the JMDC Claims Database

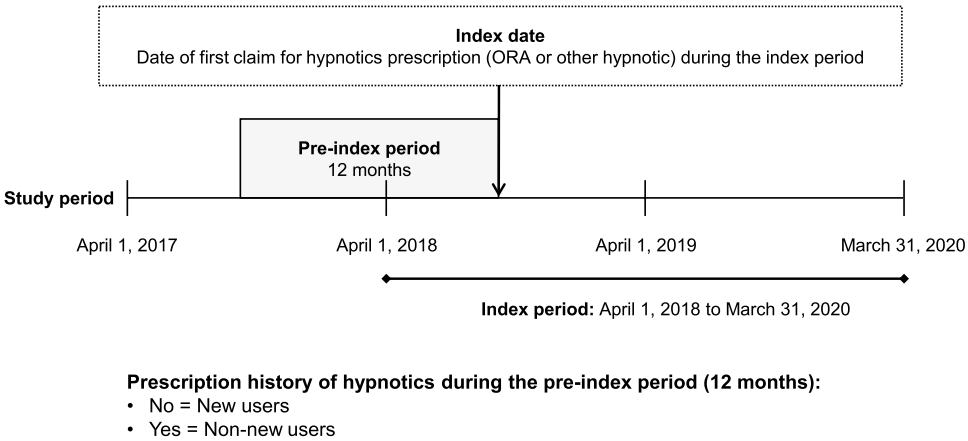

Fig. 2 Study definitions. *ORA* orexin receptor antagonist

bedtime administration. In the present study, patients who were prescribed hypnotics as *pro re nata* only at the index date and patients with overlapping prescriptions for hypnotics from two or more physicians at the index date were not analyzed.

Patients were classified as new users of hypnotics if they had no hypnotics prescription history during the 12-month pre-index period or as non-new users if they had any history of hypnotics prescription during the pre-index period (Fig. 2). New and non-new users of hypnotics were further divided into two groups (users prescribed ORA and users prescribed other hypnotics). In the study period, suvorexant was the only ORA available in Japan.

2.3 Hypnotics

Table 1 lists the oral hypnotics that were approved for the management of insomnia in Japan during the study period. We only analyzed hypnotics that were prescribed for bedtime use. Drugs such as etizolam and nitrazepam, which are approved for the treatment of both anxiety and insomnia, were also considered as hypnotics if they were prescribed for bedtime use.

2.4 Data Analysis

As in our previous study [12], we extracted the following data from the JMDC Claims Database: patient

demographics (age, sex, medical specialty, clinical setting), prescription information (name of each drug prescribed and the date of prescription), and diagnosis of psychiatric comorbidities for the present analysis. The medical specialty was defined based on the institution type as psychiatry (hospital or clinic with a primary specialty of psychiatry), general practice (GP; clinic with a primary specialty other than psychiatry), or others (hospital with a primary specialty other than psychiatry). The clinical setting was classified based on the number of beds as either a clinic (0–19 beds) or hospital (≥ 20 beds). The following psychiatric comorbidities (ICD-10 codes) were considered: substance use disorders (F10–F19), schizophrenia spectrum disorders (F20–F29), bipolar disorders (F30, F31), depressive disorders (F32, F33), anxiety disorders (F40–F42), neurocognitive disorders (F00, G30), and other psychiatric comorbidities (F00–F99, except for the psychiatric diseases designated above). We limited the analysis of neurocognitive disorders to patients with Alzheimer's disease. These variables were analyzed descriptively for patients prescribed ORA (as a single agent or in combination with other hypnotics) or other hypnotics at the index date for new and non-new users of hypnotics separately. Continuous variables were summarized using the mean and standard deviation (SD), and 95% confidence intervals (CI), while categorical variables were summarized using frequencies and percentages.

We also performed multivariable logistic regression to identify potential factors associated with ORA prescriptions at the index date in new and non-new users separately, with results expressed as odds ratios (OR) with 95% CI. The independent variables included in this model were patient demographics, psychiatric comorbidities, and history of ORA prescription (for non-new users). The dependent variable was the presence or absence of an ORA prescription at the index date.

All data analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA).

Table 1 Insomnia medications included in the analysis

Generic name	ATC code
Orexin receptor antagonist[a]	
Suvorexant	N05CM19
Other hypnotics	
Benzodiazepines	
Flurazepam	N05CD01
Quazepam	N05CD10
Haloxazolam	–
Nitrazepam	N05CD02
Flunitrazepam	N05CD03
Estazolam	N05CD04
Nimetazepam	–
Lormetazepam	N05CD06
Brotizolam	N05CD09
Etizolam	N05BA19
Rilmazafone hydrochloride	–
Triazolam	N05CD05
Non-benzodiazepines (z-drugs)	
Zopiclone	N05CF01
Zolpidem tartrate	N05CF02
Eszopiclone	N05CF04
Melatonin receptor agonist	
Ramelteon	N05CH02
Other approved hypnotics	
Phenobarbital	N03AA02
Pentobarbital calcium	N05CA01
Amobarbital	N05CA02
Barbital	N05CA04
Chloral hydrate	N05CC01
Bromovalerylurea	N05CM03
Triclofos sodium	N05CM07

ATC Anatomical Therapeutic Chemical

[a]Lemborexant was not available in Japan in the study period

3 Results

3.1 Patient Characteristics

Of 215,796 patients prescribed one or more hypnotic associated with a diagnosis of insomnia (G470) between April 1, 2018 and March 31, 2020, a total of 147,518 satisfied the eligibility criteria (Fig. 1). Of these, 58,907 were classified as new users of hypnotics (no prescription for a hypnotic in the 12-month pre-index period) and 88,611 were classified as non-new users (prescribed a hypnotic in the 12-month pre-index period).

3.2 ORA Use Among New Users of Hypnotics

Among 58,907 new users, 11,589 (19.7%) were prescribed ORA at the index date; the other 47,318 patients were prescribed hypnotic(s) other than ORA. The characteristics of new users are summarized in Table 2. The characteristics of patients prescribed ORA or other hypnotics were generally similar, with a mean ± SD age of 44.6 ± 13.0 and 44.6 ± 12.9 years, respectively. Of patients prescribed ORA, 42.5% were female and 57.5% were male, while the proportion of female patients prescribed other hypnotics was slightly higher than those prescribed ORA (46.5% female and 53.5% male).

Depressive disorders (16.8%) and anxiety disorders (10.7%) were the most common psychiatric comorbidities in patients prescribed ORA, with similar values for patients prescribed other hypnotics (depressive disorders: 15.2%; anxiety disorders: 10.7%).

Multivariable logistic regression analysis (Fig. 3) revealed that the odds of ORA prescription were significantly greater among males (vs females; OR 1.17, 95% CI 1.12–1.22) and patients with bipolar disorders (vs none; OR 1.36, 95% CI 1.20–1.55). Patients treated at a clinic (vs hospital; OR 0.75, 95% CI 0.70–0.82) had lower odds of ORA prescription. Age, psychiatric comorbidities other than bipolar disorders, and psychiatry as the medical specialty were not significantly associated with ORA prescriptions among new users.

3.3 ORA Use Among Non-New Users of Hypnotics

Of 88,611 non-new users, 15,504 were prescribed ORA at the index date and 73,107 were prescribed other hypnotics. Their baseline characteristics are summarized in Table 3. The mean ± SD age of patients prescribed ORA was slightly lower (47.6 ± 12.5 years) than that of patients prescribed other hypnotics (49.8 ± 11.9 years), with slight differences in the age distribution. Overall, 46.9% and 53.1% of patients prescribed ORA were females and males, respectively. The respective values for patients prescribed other hypnotics were 47.3% and 52.7%. All of the psychiatric comorbidities assessed in the present study were slightly more frequent among patients prescribed ORA than in patients prescribed other hypnotics.

Table 2 Demographic characteristics of new users

	Prescribed ORA *N* = 11,589	Prescribed other hypnotics *N* = 47,318
Age, years		
Mean ± SD [95% CI]	44.6 ± 13.0 [44.3–44.8]	44.6 ± 12.9 [44.5–44.8]
20–34	2946 (25.4% [24.6–26.2])	11,981 (25.3% [24.9–25.7])
35–49	4157 (35.9% [35.0–36.8])	17,043 (36.0% [35.6–36.5])
50–64	3813 (32.9% [32.0–33.8])	15,541 (32.8% [32.4–33.3])
65–74	673 (5.8% [5.4–6.2])	2753 (5.8% [5.6–6.0])
Sex		
Female	4929 (42.5% [41.6–43.4])	22,016 (46.5% [46.1–47.0])
Male	6660 (57.5% [56.6–58.4])	25,302 (53.5% [53.0–53.9])
Psychiatric comorbidities		
Depressive disorders	1943 (16.8% [16.1–17.5])	7174 (15.2% [14.8–15.5])
Anxiety disorders	1245 (10.7% [10.2–11.3])	5058 (10.7% [10.4–11.0])
Schizophrenia spectrum disorders	473 (4.1% [3.7–4.5])	1628 (3.4% [3.3–3.6])
Bipolar disorders	366 (3.2% [2.8–3.5])	1026 (2.2% [2.0–2.3])
Substance use disorders	119 (1.0% [0.9–1.2])	461 (1.0% [0.9–1.1])
Neurocognitive disorders[a]	12 (0.1% [0.1–0.2])	47 (0.1% [0.1–0.1])
Other psychiatric comorbidities	1892 (16.3% [15.7–17.0])	7139 (15.1% [14.8–15.4])
Medical specialty		
Psychiatry[b]	3718 (32.1% [31.2–32.9])	13,655 (28.9% [28.4–29.3])
GP[c]	6991 (60.3% [59.4–61.2])	29,478 (62.3% [61.9–62.7])
Others[d]	880 (7.6% [7.1–8.1])	4185 (8.8% [8.6–9.1])
Clinical setting/number of beds		
Clinic (≤ 19 beds)	9595 (82.8% [82.1–83.5])	39,815 (84.1% [83.8–84.5])
Hospital (≥ 20 beds)	1994 (17.2% [16.5–17.9])	7503 (15.9% [15.5–16.2])

Values are *n* (% [95% confidence interval]) unless otherwise specified

Suvorexant (ORA) could be prescribed as a single agent or in combination with other hypnotics

GP general practice, *ORA* orexin receptor antagonist, *SD* standard deviation

[a]We limited the analysis of neurocognitive disorders to patients with Alzheimer's disease

[b]Hospital or clinic with a primary specialty of psychiatry

[c]Hospital with a primary specialty other than psychiatry

[d]Clinic with a primary specialty other than psychiatry

Multivariable logistic regression analysis (Fig. 4) revealed that patients with most of the psychiatric comorbidities examined, including neurocognitive disorders (Alzheimer's disease) (OR 1.64, 95% CI 1.15–2.35), substance use disorders (OR 1.19, 95% CI 1.05–1.35), bipolar disorders (OR 1.14, 95% CI 1.07–1.22), schizophrenia spectrum disorders (OR 1.07, 95% CI 1.01–1.14), or anxiety disorders (OR 1.05, 95% CI 1.00–1.10), had greater odds of ORA prescription at the index date. Patients with a history of ORA prescription also had greater odds of ORA prescription (OR 18.86, 95% CI 17.88–19.89). Patients aged 35–49 (OR 0.80, 95% CI 0.75–0.85), 50–64 (OR 0.74, 95% CI 0.69–0.78), or 65–74 years (OR 0.69, 95% CI 0.63–0.75) had lower odds of ORA prescription compared with patients aged 20–34 years. Furthermore, patients treated in psychiatry (vs GP; OR 0.92, 95% CI 0.87–0.97) and patients treated at clinics (vs hospital; OR 0.82, 95% CI 0.77–0.88) had lower odds of ORA prescription.

4 Discussion

The present findings provide further insight and expand on our earlier study, in which we documented increasing ORA prescriptions among new and long-term users of hypnotics [12]. To our knowledge, this is the first study to evaluate the factors associated with ORA prescriptions for patients with insomnia in Japan. This study revealed that, among new hypnotic users, the age or the presence or absence of psychiatric disorders (except for bipolar disorder) were not associated with ORA prescription at the index date, suggesting that physicians in Japan are more likely to prescribe ORA regardless of their patients' psychiatric comorbidities, when selecting ORA as the first hypnotic for new users. In addition, for non-new hypnotic users, we observed significant positive associations between the presence of most of the psychiatric comorbidities examined (substance use disorders, bipolar disorders, schizophrenia spectrum disorders, anxiety disorders, and neurocognitive disorders [Alzheimer's disease]) and ORA prescription.

The patterns observed in this study may be driven by recent studies documenting the real-world use of ORA among patients with insomnia, including those with psychiatric comorbidities. For example, results of the post-marketing survey of suvorexant in Japan conducted between 2015 and 2017 showed that suvorexant is generally well tolerated by both younger adults and older patients with heterogeneous background demographic characteristics, consisting of new and non-new users, in real-world clinical settings [13, 19, 20]. The survey included patients with a variety of psychiatric comorbidities (schizophrenia, depression, manic-depressive disorder, anxiety disorder, and dementia) who were excluded from the pre-approval clinical trials [21]. Those findings likely prompted broader use of ORA in clinical practice for the period analyzed in our study (April 1, 2018–March 31, 2020), and likely supported the physicians' choice of prescribing ORA to patients with psychiatric comorbidities as well as patients without them. In fact,

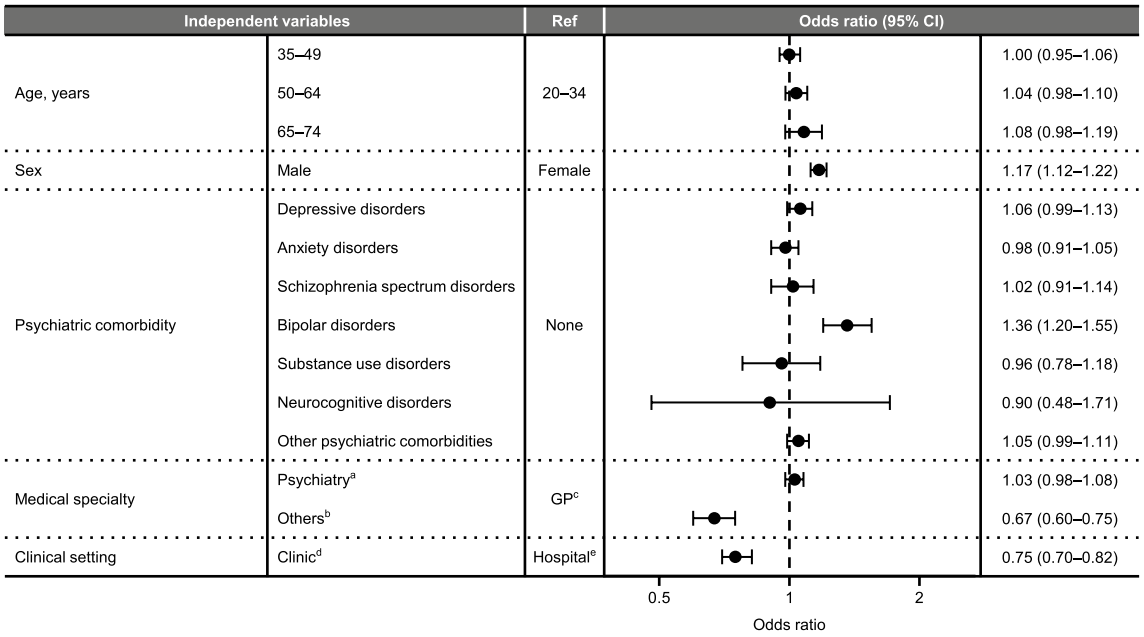

Fig. 3 Associations between demographic factors and ORA prescriptions in new users. *CI* confidence interval, *GP* general practice, *ORA* orexin receptor antagonist, *Ref* reference. [a]Hospital or clinic with a primary specialty of psychiatry. [b]Hospital with a primary specialty other than psychiatry. [c]Clinic with a primary specialty other than psychiatry. [d]Facility with 0–19 beds. [e]Facility with ≥ 20 beds

Table 3 Demographic characteristics of non-new users

	Prescribed ORA $N=15,504$	Prescribed other hypnotics $N=73,107$
Age, years		
Mean ± SD [95% CI]	47.6 ± 12.5 [47.4–47.8]	49.8 ± 11.9 [49.7–49.9]
20–34	2648 (17.1% [16.5–17.7])	8868 (12.1% [11.9–12.4])
35–49	5558 (35.8% [35.1–36.6])	24,688 (33.8% [33.4–34.1])
50–64	5991 (38.6% [37.9–39.4])	31,698 (43.4% [43.0–43.7])
65–74	1307 (8.4% [8.0–8.9])	7853 (10.7% [10.5–11.0])
Sex		
Female	7272 (46.9% [46.1–47.7])	34,604 (47.3% [47.0–47.7])
Male	8232 (53.1% [52.3–53.9])	38,503 (52.7% [52.3–53.0])
Psychiatric comorbidities		
Depressive disorders	7798 (50.3% [49.5–51.1])	32,130 (43.9% [43.6–44.3])
Anxiety disorders	3824 (24.7% [24.0–25.4])	16,199 (22.2% [21.9–22.5])
Schizophrenia spectrum disorders	3199 (20.6% [20.0–21.3])	10,858 (14.9% [14.6–15.1])
Bipolar disorders	2266 (14.6% [14.1–15.2])	7080 (9.7% [9.5–9.9])
Substance use disorders	462 (3.0% [2.7–3.3])	1560 (2.1% [2.0–2.2])
Neurocognitive disorders[a]	56 (0.4% [0.3–0.5])	154 (0.2% [0.2–0.2])
Other psychiatric comorbidities	6272 (40.5% [39.7–41.2])	24,454 (33.4% [33.1–33.8])
Medical specialty		
Psychiatry[b]	6484 (41.8% [41.0–42.6])	27,050 (37.0% [36.7–37.4])
GP[c]	7464 (48.1% [47.4–48.9])	38,093 (52.1% [51.7–52.5])
Others[d]	1556 (10.0% [9.6–10.5])	7964 (10.9% [10.7–11.1])
Clinical setting/number of beds		
Clinic (≤ 19 beds)	11,323 (73.0% [72.3–73.7])	55,397 (75.8% [75.5–76.1])
Hospital (≥ 20 beds)	4181 (27.0% [26.3–27.7])	17,710 (24.2% [23.9–24.5])
History of ORA prescription	6040 (39.0% [38.2–39.7])	2310 (3.2% [3.0–3.3])

Values are *n* (% [95% confidence interval]) unless otherwise specified

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[d]Clinic with a primary specialty other than psychiatry

a recent study of Japanese claims data documented a higher rate of psychiatric comorbidities in those prescribed suvorexant than in those prescribed z-drugs [22]. The authors suggested that, due to its novel mode of action (MOA), suvorexant was preferably prescribed by physicians with a high level of sleep expertise, such as psychiatrists who have more opportunities to treat insomnia in patients with psychiatric comorbidities.

In a recent analysis of potential channeling of suvorexant compared with other FDA-approved hypnotics in a US-based claims database, it was found that new users of suvorexant were older, included a greater proportion of females, and had a higher percentage of psychiatric comorbidities including depression and anxiety [23]. Interestingly, there are several potential differences between that study and the present study. In particular, we found patients with psychiatric comorbidities had greater odds for ORA prescriptions among non-new users, although not among new users. The ORs for ORA prescription tended to increase by age category among new users but did not reach statistical significance. However, the negative association between age and ORA prescriptions among non-new users in the present study differed from the finding of the channeling study [23]. This might be explained by differences in clinical practice for managing insomnia patients between the US and Japan. Compared with the physicians in the US, physicians in Japan tend to prescribe ORA to insomnia patients (new users) regardless of psychiatric comorbidities. In younger non-new users with psychiatric comorbidities, the physicians in Japan may be shifting from routine prescription for BZD/z-drugs to an ORA as a hypnotic with a different MOA, or adding an ORA to existing hypnotics. However, for older

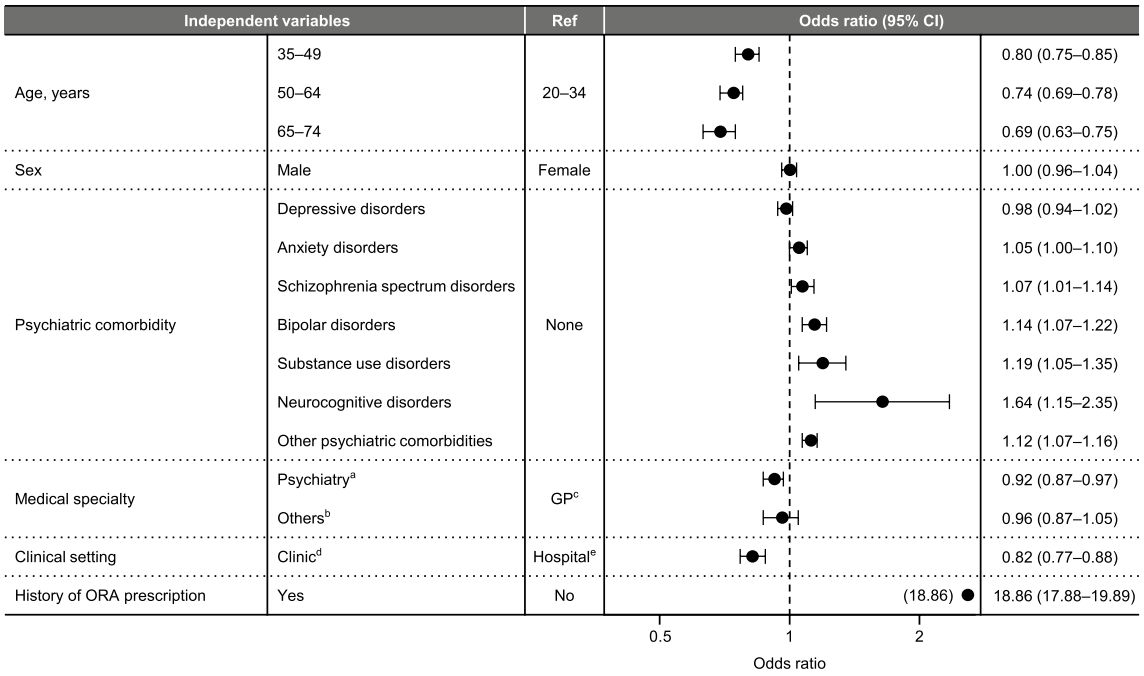

Fig. 4 Associations between demographic factors and ORA prescriptions in non-new users. *CI* confidence interval, *GP* general practice, *ORA* orexin receptor antagonist, *Ref* reference. [a]Hospital or clinic with a primary specialty of psychiatry. [b]Hospital with a primary specialty other than psychiatry. [c]Clinic with a primary specialty other than psychiatry. [d]Facility with 0–19 beds. [e]Facility with ≥ 20 beds

non-new patients with psychiatric comorbidities, physicians in Japan may prefer to continue the hypnotics they have been using other than ORA. Further accumulation of data on the risk–benefit profiles of hypnotics in older patients may be useful for supporting treatment decisions in real-world settings. It should be noted that the divergence in the results might be at least partly due to the differences in the characteristics of the databases used in that study and our study. The JMDC Claims Database has a limited number of people aged ≥ 65 years and none aged ≥ 75 years. The mean age of patients newly prescribed ORA was greater in the US study (65.0 ± 14.7 years) than in our study (44.6 ± 13.0 years), which might contribute to the non-significant OR for age among new users in our study.

Several prospective clinical studies have investigated the use of ORA for the treatment of insomnia in Japanese patients with psychiatric disorders. For example, Kishi et al. [15], Nakamura and Nagamine [24], and Ueda [16] have reported the clinical usefulness of suvorexant in insomnia patients with various psychiatric comorbidities, including depressive disorders, bipolar disorders, neurocognitive disorders (dementia), and schizophrenia spectrum disorders. It is well known that sleep disturbances impose a huge burden on patients with neurocognitive disorders such as Alzheimer's disease [25]. Randomized clinical trials have examined the role of suvorexant in patients with Alzheimer's disease and insomnia. In a 4-week study of patients with mild-to-moderate Alzheimer's disease (aged ≥ 50 years) and insomnia, Herring et al. reported that suvorexant improved objective total sleep time and sleep maintenance compared with placebo [14]. Similar findings were observed in a Japanese study [26]. These findings, together with the results of the post-marketing survey of suvorexant in Japan, support our data showing that neurocognitive disorders (Alzheimer's disease) could be a factor that is positively associated with ORA prescriptions among non-new users of hypnotics. In addition, it may also reflect the current clinical situation showing that physicians are trying to reduce inappropriate use of BZD/z-drugs in elderly insomnia patients, resulting in prescriptions of hypnotics with different MOAs. Regarding other substance use disorders, a study has revealed a beneficial effect of suvorexant in patients with these disorders [27], and a phase II trial is also planned to investigate the effectiveness of suvorexant for patients with alcohol use disorder and comorbid insomnia [28, 29]. Supporting this possibility, the potential involvement of the orexin system in drug addiction/substance use disorders was demonstrated in numerous animal studies [30, 31]. As described above, several studies have described the clinical usefulness of suvorexant in various insomnia patient groups, including those with various psychiatric comorbidities. However, to our knowledge, there were no studies that specifically investigated the effects of suvorexant on insomnia in patients with depression, bipolar

disorder (except for one case report [32]), anxiety disorder, or schizophrenia (except for one case report [33]) at the time of conducting our analyses. Very recently, Shigetsura et al. reported a new finding that switching from BZD to suvorexant was associated with a significant improvement of insomnia in patients with major depressive disorder [34]. Overall, the findings published to date suggest that ORA is an effective and tolerable treatment option for insomnia in patients with a wide variety of psychiatric comorbidities, and that physicians may be becoming more familiar with their use in this setting. Further accumulation of evidence for ORA in insomnia patients with psychiatric comorbidities will likely influence the prescribing patterns for hypnotics in the future.

Some limitations warrant mention, most of which were also described in our prior report [12]. First, the JMDC Claims Database primarily includes employed, working-age people and their families with a limited number of people aged ≥ 65 years and none aged ≥ 75 years. Therefore, older individuals are underrepresented compared with the total Japanese population. Also, because the data stored in the JMDC Claims Database are intended for insurance purposes rather than research, the data might be contaminated by misclassification of ICD-10 codes or diagnosis for receipts to receive reimbursements. Second, we only considered hypnotics prescribed for once-daily administration at bedtime. This definition was designed to reduce the number of patients prescribed BZDs for other indications such as anxiety disorders, but conversely, it may not be able to detect patients prescribed with hypnotics for the treatment of both insomnia and anxiety disorders. Third, psychiatry, as a category of medical specialty, was defined as a medical institution that considered psychiatry as the primary department in the JMDC Claims Database (based on the information of medical institutions managed by the Regional Bureau of Health and Welfare). Some medical institutions that considered psychiatry as a non-primary department might be included in the category 'others'. Therefore, data for 'psychiatry' might be underestimated. Fourth, we should acknowledge the possibility that some users with a history of hypnotics treatment but who received no prescription of hypnotics in the 12-month pre-index period were included as new users. In addition, for non-new users, the number of prescriptions for ORA or other hypnotics received in the pre-index period (or the duration of prescription) was not considered. Finally, we cannot exclude the possibility that other clinically relevant factors including other clinical diagnoses (e.g., bone fracture) not captured in the JMDC Claims Database for the present study could contribute to the decisions to prescribe an ORA or other hypnotics.

5 Conclusion

This is the first study to determine which factors are associated with prescription of ORA in real-world clinical practice in Japan. We found that, among new users of hypnotics, physicians in Japan are more likely to prescribe ORA regardless of their patients′ psychiatric comorbidities, when selecting ORA as the first hypnotic. However, we also found significant positive associations between the presence of most of the psychiatric comorbidities examined and ORA prescription among non-new users of hypnotics. Our findings could help guide appropriate insomnia treatment using ORAs. Further research regarding prescriptions of ORAs, particularly within elderly patients with insomnia, is needed.

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Declarations

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Conflict of interest Shoki Okuda, Yukiko Yanagida, and Shigeru Tokita are employees of MSD K.K., Tokyo, Japan, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. Zaina P. Qureshi was an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may have owned stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA at the time of the study. Yuji Homma is an employee of JMDC Inc. and Chie Ito was an employee of JMDC Inc. at the time of the study.

Ethics approval This study utilized commercially available de-identified secondary data from the JMDC Claims Database, which contains a significant level of protection against the release of personal information to outside entities. Furthermore, all analyses were conducted by JMDC Inc., and the project deliverables comprised aggregated data, as descriptive statistics in the form of tables and figures. Patient counts below five were reported as '< 5' to protect privacy. No reporting of individual cases to regulatory agencies was planned as part of this retrospective observational database analysis. The Japanese ethical guidelines for medical research do not require ethics review of studies using a de-identified database comprising previously collected secondary data (Notified 23 March 2021, amended 10 March 2022: Ministry of Education, Culture, Sports, Science and Technology; Ministry of Health, Labour and Welfare; and Ministry of Economy, Trade and Industry). Therefore, no ethics review or Institutional Review Board review was required for this study.

Consent to participate In accordance with Japanese guidelines, informed consent was not required for this study using a de-identified database comprising previously collected secondary data.

Consent for publication Not applicable.

Data availability The JMDC Claims Database analyzed in this study (analysis dataset) is not publicly accessible, and the data cannot be shared with external researchers according to the contract with JMDC Inc. Please contact JMDC Inc. (https://www.jmdc.co.jp) for inquiries about access to the dataset used in this study.

Code availability Not applicable.

Author contributions Shoki Okuda, Yukiko Yanagida, Zaina P. Qureshi, and Shigeru Tokita conceived the study. Shoki Okuda, Chie Ito, and Yuji Homma designed the study and data analysis plan. Chie Ito and Yuji Homma analyzed the data. Zaina P. Qureshi and Shigeru Tokita contributed to study design. All authors contributed to interpretation of data, reviewed the manuscript, and approved the final version of the manuscript. Shoki Okuda is the guarantor and accepts full responsibility for the work.

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