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ORIGINAL RESEARCH

Is Agomelatine Associated with Less Sedative-Hypnotic Usage in Patients with Major Depressive Disorder? A Nationwide, Population-Based Study

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Background: To examine the association between the usage of agomelatine in patients with major depressive disorder and the usage of sedative-hypnotics.

Methods: This population-based, cross-sectional study used Taiwan's National Health Insurance Research Database (NHIRD) between 2012 and 2015. The agomelatine-only group and matched control (1:3) with the usage of other antidepressants were enrolled. The association between the usage of the agomelatine and other antidepressants and the usage of sedative-hypnotics in the patients were also assessed.

Results: A total of 7961 subjects were enrolled comprising 1985 with the usage of agomelatine only, and 5976 with other antidepressants. In the present study, a total of 3322 subjects who used the sedative-hypnotics were recorded, with 811 (40.86%) from the agomelatine-only group and 2511 (42.02%) from the non-agomelatine group, which have used sedative-hypnotics. After adjusting for covariates, the odds ratio (OR) of the usage of sedative-hypnotics in the agomelatine only-group was 0.892 (95% CI: 0.306–1.601, $p = 0.533$), in comparison to the controls, and the relative risk (RR) of the usage of sedative-hypnotics in the agomelatine only-group was 0.910 (95% CI: 0.312–1.633, $p = 0.520$), in comparison to the controls. No matter as to whether the treatment duration was <30 days or ≧ 30 days of agomelatine treatment was not associated with the increased usage of the sedative-hypnotics. The OR or RR for usage of the sedative-hypnotics was associated with the Charlson Comorbidity Index (CCI) scores as 2, 3, and ≧ 4, and the medical care from the medical center and regional hospital.

Conclusion: Patients with the agomelatine-only group were not associated with the usage of sedative-hypnotics in comparison to the group using other antidepressants.

Keywords: agomelatine, insomnia, antidepressant, major depressive disorder, National Health Insurance Research Database

Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders in adults, with significant burdens for the patients and the cost of treatment.[1,2] Insomnia is one of the most common symptoms in MDD, and one study has reported that the prevalence rates for insomnia in MDD were 48.5%.[3] Sedative-hypnotics, such as benzodiazepines and Z-drugs, are widely used in patients with insomnia, and one report using Taiwan's National Health Insurance Research

Database (NHIRD) estimated that 95.5% of patients with MDD have used the sedative-hypnotics.[4] However, sedative-hypnotics have several disadvantages, such as the associations with the risk of falling-related injuries,[5] suicide,[6] dementia,[7,8] and some respiratory or neurodegenerative diseases.[9–11] In addition, benzodiazepines are frequently used to treat insomnia; however, the side effects might include a withdrawal syndrome with rapid eye movement (REM) rebound.[12]

Antidepressants are widely used in the treatment of MDD. In addition, antidepressants have several effects on sleep: in short-term treatment, many activating antidepressant effects may disrupt sleep, while others with sedative properties rapidly improve sleep; however, all antidepressants should normalize sleep in the long-term treatment.[13] Agomelatine, as a novel antidepressant for the treatment of MDD, could quickly improve the disturbed sleep-wake cycles,[14] sleep efficiency, and correcting the circadian rhythm abnormalities,[15] with a promising role for the treatment of sleep disorders associated with MDD.[16] In addition, the melatonin (MT) receptor agonists are now appearing as the new promising treatment options for sleep and circadian-rhythm-related disorders, such as agomelatine and ramelteon.[17] Being the MT_1 and MT_2 receptors agonists, agomelatine is also an antagonist that affects the 5-hydroxytryptamine-2C ($5HT_{2c}$) receptors. Since agomelatine acts on the suprachiasmatic nucleus, hippocampus, frontal cortex, and the striatum, it could lead to the improvement of both the sleep and mood.[18,19] There are distinctive differential binding affinities to MT_1 versus MT_2: Agomelatine binds to MT_1 and MT_2 receptors with approximately equal affinity and additional antagonist properties at the $5\text{-}HT_{2c}$ receptors, and ramelteon exhibits a 10-fold greater affinity for MT_1 than MT_2.[20,21] This might explain why there are differences in the effect of facilitations in sleep-onset between these two medications. However, problems of the sleep-wake cycle and circadian rhythm would be corrected by the usage of agomelatine.[15,16] However, there has been little research done on the association between agomelatine and the usage of sedative-hypnotics. This study aimed to test the hypothesis as to whether being treated with agomelatine is less likely to be co-treated with sedative hypnotic agents.

Materials and Methods

Data Sources

The National Health Insurance (NHI) Program was launched in Taiwan in 1995, and as of June 2009, included contracts with 97% of the medical providers with approximately 23 million beneficiaries, or more than 99% of the entire population.[22] The NHIRD, which contains all the claims data of the beneficiaries, uses the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to record the diagnoses,[23] and were widely used in the medical studies with good diagnostic validity.[24] The details of the program have been documented in previous studies.[25–32] In the NHIRD, clinicians perform the coding based on the clinical diagnoses of the patients and according to the standards promulgated by the NHI Administration. Licensed medical records technicians would verify the coding before claiming the reimbursements.[24] Furthermore, there is an audit mechanism to check the data of outpatient and emergency departments and hospitalization to ensure the accuracy of the data in the NHI Administration, in which the records were reviewed as 1 in 100 ambulatory care visits and 1 in 20 in-patient claims, so as to verify the accuracy of the diagnoses.[33] Other efforts to ensure data validity including algorithms developed to identify targeted diagnosis and treatment by applying multiple criteria, and validation studies. A continuous and concerted action by the NHI and the researchers is required to address the issue.[24] In Taiwan, agomelatine has been licensed since 2012. Therefore, a subset of the NHIRD, the Longitudinal Health Insurance Database (LHID) of a two million randomized sampled population between 2012 and 2015, was used to study the association between the agomelatine-only patients and the other antidepressant-controls, and the odds ratio (OR) and relative risk (RR) of the usage of sedative-hypnotics. In Taiwan, the dosage range of agomelatine is 25 mg a day at bedtime and then up-titrated to a maximum dose of 50 mg a day; however, an even higher dosage is not allowed.[34] The present study used the NHIRD to identify the patients with the usage of agomelatine and other antidepressants.

Ethical Approval

This study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). This study was approved by the Institutional Review Board (IRB) of the Tri-Service General Hospital (TSGH). The TSGH IRB waived the need of individual consents since all the identification data were encrypted in the NHIRD (IRB No. B202005105).

Study Design and Sampled Participants

This study was of a population-based, cross-sectional design. Patients with MDD (ICD-9-CM codes: 296.2x,

296.3x), who had used different classes of antidepressants (Table S1), were enrolled from the LHID between January 1, 2012, and December 31, 2015. The group entry date was defined as the first prescription date of agomelatine or other antidepressants during the study period. The cases and the control subjects were selected 1:3 by the estimated propensity score matched by sex, age, and index-year. The usage of the sedative-hypnotics was recorded in this study. The study outcome was the OR for the usage of the sedative-hypnotics.

Covariates

The covariates included sex, age, marital status, educational years (<12 years and ≥12 years), monthly insurance premiums (in New Taiwan Dollars [NT$]; <18,000, 18,000–34,999, ≥35,000), geographical locations of residence (north, center, south, and east of Taiwan), urbanization levels of residence (levels 1 to 4), seasons of help-seeking, and levels of medical care. We used the Charlson Comorbidity Index, which categorizes the comorbidities using the ICD-9-CM codes, scores each comorbidity category, and combines all the scores to calculate a single comorbidity score, with the scores as CCI, 0, 1, 2, 3, ≥4. A score of zero indicated that no comorbidities were found, and higher scores indicated the higher comorbidity burdens.[35–37] Figure 1 presents a detailed flowchart regarding the subject selection and the study design.

Statistical Analysis

The chi-square test was adapted to examine the differences in the distributions between the usage of antidepressants and the OR and RR of the usage of sedative-hypnotics. Multivariable logistic regression was employed to calculate the impact of demographic characteristics, types, and durations of antidepressants on the OR of the usage of sedative-hypnotics. The level of significance (a two-tailed p value) was maintained at <0.05 for all statistical analyses. The statistical analyses were performed using the software SPSS 22.0.

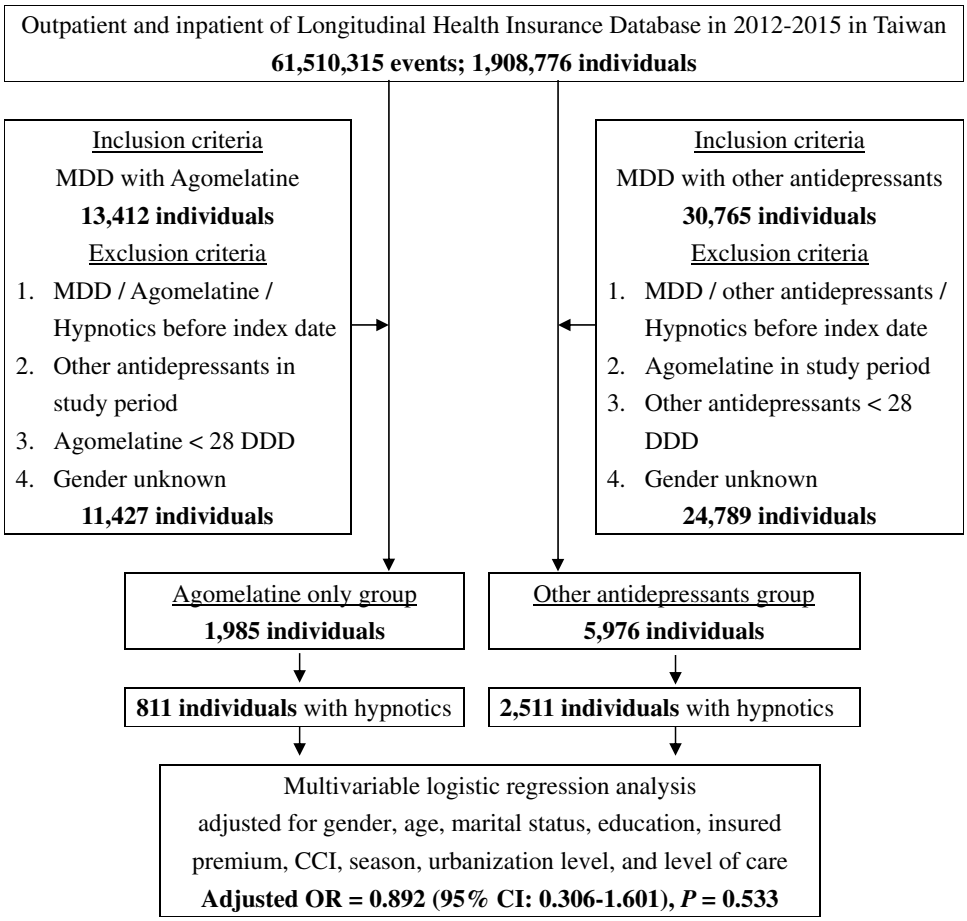

Figure 1 The flowchart of study sample selection (cross-section study).

Results

Sample Characteristics

A total of 7961 subjects were enrolled comprising 1985 with the usage of agomelatine only and 5976 with other antidepressants. Table 1 shows the sex, age, marital status, monthly insurance premiums, education, CCI scores, seasons of the medical help-seeking, urbanization, locations of residence, for the agomelatine only-patients, and the other antidepressant-controls. When compared to the other antidepressants-controls, the agomelatine only-patients tended to have the lower CCI scores. The agomelatine only-patients tended to have higher rates of living in the middle and south of Taiwan and seeking help in the medical centers than the control groups.

Odds Ratio Analysis of the Usage of Sedative-Hypnotics in Agomelatine Only-Patients

Table 2 shows the multivariable logistic regression analysis of the factors associated with the risk of the usage of sedative-hypnotics. The crude OR was 0.986 (95% CI: 0.423–1.775, $p = 0.452$), after adjusting for the covariates, the adjusted OR was 0.892 (95% CI: 0.306–1.601, $p = 0.533$). There were increased ORs for the usage of the sedative-hypnotics that were associated with the CCI scores as 2, 3, and ≧ 4, and the medical care from the medical center and regional hospital.

Relative Risk Analysis of the Usage of Sedative-Hypnotics in Agomelatine Only-Patients

Table 3 shows the relative risk analysis of the factors associated with the risk of the usage of sedative-hypnotics. The crude RR was 0.996 (95% CI: 0.425–0.755, $p = 0.452$), after adjusting for the covariates, the adjusted RR was 0.910 (95% CI: 0.312–1.633, $p = 0.520$). There were increased RRs for the usage of the sedative-hypnotics that were associated with the CCI scores as 2, 3, and ≧ 4, and the medical care from the medical center and regional hospital.

Odds Ratio and Relative Risk Analysis of the Usage of Sedative-Hypnotics in Agomelatine Only-Patients

The association between the agomelatine only-group and other antidepressants was insignificant for the usage of

Table 1 Characteristics of Two Groups in the Present Study

Antidepressants	Agomelatine Only		Other Antidepressants		P
Variables	**n**	**%**	**n**	**%**	
Total	1985	24.93	5976	75.07	
Hypnotics					0.363
Without	1174	59.14	3465	57.98	
With	811	40.86	2511	42.02	
Sex					0.663
Male	1016	51.18	3025	50.62	
Female	969	48.82	2951	49.38	
Age (years)	45.97 ± 19.76		40.97 ± 18.32		<0.001
Marital status					0.828
Without	961	48.41	2910	48.69	
With	1024	51.59	3066	51.31	
Education (years)					0.871
<12	988	49.77	2987	49.98	
≧12	997	50.23	2989	50.02	
Insured premium (NT$)					0.782
<18,000	1778	89.57	5331	89.21	
18,000–34,999	164	8.26	522	8.73	
≧35,000	43	2.17	123	2.06	
CCI					<0.001
0	798	40.20	1882	31.49	
1	531	26.75	1495	25.02	
2	309	15.57	1204	20.15	
3	297	14.96	1229	20.57	
≧4	50	2.52	166	2.78	
Season					0.523
Spring (March–May)	488	24.58	1426	23.86	
Summer (June–August)	520	26.20	1668	27.91	
Autumn (September–November)	511	25.74	1516	25.37	
Winter (December–February)	466	23.48	1366	22.86	
Location					<0.001
Northern Taiwan	735	37.03	2312	38.69	
Middle Taiwan	468	23.58	1213	20.30	
Southern Taiwan	493	24.84	1264	21.15	
Eastern Taiwan	280	14.11	1100	18.41	
Outlying islands	9	0.45	87	1.46	
Urbanization level					0.235
1 (The highest)	701	35.31	2221	37.17	
2	812	40.91	2420	40.50	
3	211	10.63	555	9.29	
4 (The lowest)	261	13.15	780	13.05	

(*Continued*)

Table 1 (Continued).

Antidepressants	Agomelatine Only		Other Antidepressants		P
Variables	**n**	**%**	**n**	**%**	
Level of care					<0.001
Medical center	768	38.69	1813	30.34	
Regional hospital	811	40.86	2876	48.13	
Local hospital	406	20.45	1287	21.54	

Note: P: Chi-square/Fisher exact test on category variables and t-test on continue variables.
Abbreviation: NT$, New Taiwan Dollars.

different treatment durations. No matter that the treatment durations were <30 days or ≧30 days of agomelatine treatment in both the OR analysis (Table 4) and the RR analysis (Table 5).

Discussion

The present study has found that being treated with agomelatine was not associated with a lower OR and RR as being co-treated with sedative hypnotic agents, even though previous studies have shown that agomelatine was beneficial to several sleep problems. Agomelatine could enhance their sleep cycle[38,39] by resynchronization of the circadian rhythm.[13,40] In addition, agomelatine is the only antidepressant with a lower likelihood of inducing insomnia.[41] Furthermore, agomelatine might be a valuable addition to the pharmacological repertoire for the treatment of alcohol dependence-associated insomnia.[42] To the best of our knowledge, this is the first nationwide, population-based study on the topic of the usage of sedative-hypnotics in the patients using agomelatine.

In the present study, the increased OR or RR for usage of the sedative-hypnotics was associated with the CCI scores as 2, 3, and ≧ 4, and the medical care from the medical center and regional hospital. This might support the previous findings that sleep disorders are prevalent in patients with more medical comorbidities[43,44] or even need a higher medical attention.[45,46] In addition, there appeared to be more middle CCI scores as 2, 3, and ≧ 4 in the other

Table 2 Factors of Sedative-Hypnotics by Using Multivariable Logistic Regression

Variables Antidepressants	Crude OR	95% CI	95% CI	*P*	Adjusted OR	95% CI	95% CI	*P*
Agomelatine only	0.986	0.423	1.775	0.452	0.892	0.306	1.601	0.533
Age (years)	1.791	1.226	2.006	0.001	1.642	1.125	1.864	0.003
CCI=2 (reference: CCI = 0)	1.240	0.986	1.302	0.062	1.286	1.003	1.482	0.048
CCI=3 (reference: CCI = 0)	1.335	1.153	1.565	<0.001	1.465	1.201	1.798	<0.001
CCI≧4 (reference: CCI = 0)	1.298	1.098	1.443	0.004	1.333	1.145	1.665	<0.001
Autumn (reference: spring)	1.997	1.232	3.375	<0.001	1.842	1.124	2.977	0.001
Level 1 (reference: level 4)	2.501	1.297	5.340	<0.001	1.642	1.065	4.435	0.027
Medical center (reference: local hospital)	3.011	2.401	4.020	<0.001	2.660	2.343	2.999	<0.001
Regional hospital (reference: local hospital)	2.066	1.564	2.868	<0.001	1.765	1.131	1.986	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; Adjusted OR, adjusted variables listed in the table; CCI, Charlson Comorbidity Index.

Table 3 Factors of Sedative-Hypnotics by Using Relative Risk Analysis

Variables Antidepressants	Crude RR	95% CI	95% CI	*P*	Adjusted RR	95% CI	95% CI	*P*
Agomelatine only	0.996	0.425	0.755	0.443	0.910	0.312	1.633	0.520
Age (years)	1.827	1.240	2.483	0.001	1.675	1.148	1.901	0.003
CCI=2 (reference: CCI = 0)	1.265	1.025	1.624	0.044	1.312	1.023	1.512	0.047
CCI=3 (reference: CCI = 0)	1.462	1.370	2.457	<0.001	1.494	1.225	1.834	<0.001
CCI≧4 (reference: CCI = 0)	1.324	1.189	2.098	0.004	1.360	1.168	1.698	<0.001
Autumn (reference: spring)	2.037	1.452	4.257	<0.001	1.879	1.147	3.037	0.001
Urbanization Level 1 (reference: level 4)	2.551	1.309	17.669	<0.001	1.675	1.086	4.524	0.026
Medical center (reference: local hospital)	3.071	2.375	5.904	<0.001	2.713	2.390	3.059	<0.001
Regional hospital (reference: local hospital)	2.107	1.986	4.256	<0.001	1.800	1.154	2.026	<0.001

Abbreviations: RR, relative risk; CI, confidence interval; Adjusted RR, adjusted variables listed in the Table 1; CCI, Charlson Comorbidity Index.

Table 4 Comparing the Odd Ratios of Hypnotics Between Agomelatine Only and Other Antidepressants by Using Multivariable Logistic Regression

DDD	Antidepressants Subgroup	Populations	Hypnotics		Agomelatine Only vs Other Antidepressants (Reference)			
		n	n	%	Adjusted OR	95% CI	95% CI	*P*
Overall	Agomelatine only	1985	811	40.86				
	Other Antidepressants, Overall	5976	2511	42.02	0.892	0.306	1.601	0.533
	TCA	2012	798	39.66	0.841	0.288	1.365	0.503
	SSRI	2352	896	38.10	0.802	0.275	1.251	0.484
	SNRI	2111	765	36.24	0.766	0.263	1.186	0.462
	NDRI	1986	872	43.91	0.935	0.321	1.456	0.550
	RIMA	2028	803	39.60	0.841	0.289	1.311	0.511
1–29	Agomelatine only	862	366	42.46				
	Other Antidepressants, Overall	2233	901	40.35	0.824	0.284	1.289	0.493
	TCA	990	355	35.86	0.732	0.249	1.144	0.432
	SSRI	1024	429	41.89	0.856	0.293	1.335	0.515
	SNRI	986	376	38.13	0.777	0.265	1.215	0.464
	NDRI	971	425	43.77	0.893	0.303	1.383	0.533
	RIMA	1011	390	38.58	0.787	0.271	1.226	0.472
≧30	Agomelatine only	1123	445	39.63				
	Other Antidepressants, Overall	3743	1610	43.01	0.940	0.322	1.462	0.563
	TCA	1022	443	43.35	0.950	0.321	1.489	0.572
	SSRI	1328	467	35.17	0.771	0.262	1.211	0.462
	SNRI	1125	389	34.58	0.753	0.258	1.186	0.451
	NDRI	1015	447	44.04	0.962	0.333	1.503	0.578
	RIMA	1017	413	40.61	0.888	0.301	1.397	0.530

Abbreviations: DDD, days of drugs used; RR, relative risk; CI, confidence interval; Adjusted RR, adjusted variables listed in Table 2; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; NDRI, norepinephrine dopamine reuptake inhibitor; RIMA, reversible monoamine oxidase inhibitor.

antidepressant group. There is no study, as yet, for the agomelatine treatment for depression in people with physical comorbidities. The reason we speculate is that physicians tended to prescribe familiar antidepressants, which were frequently used for patients with both physical illness and depression,[47,48] instead of agomelatine, which has been licensed since 2012 in Taiwan.

High pressure of life accompanying living in the higher urbanized area could be related to the association between the agomelatine group in the higher urbanized area and the increased OR and RR of the usage of the sedative-hypnotics.[49,50] The agomelatine group who sought medical help in the autumn was associated with a higher risk of using the sedative-hypnotics, and this might well be related to the fact that sleep disturbance could be associated with the significant shortening of exposure to sunlight in this season.[51] In addition, antidepressant treatment-emergent insomnia is a critical issue in the treatment of depression.[13,40] Thus, the study aims to address a topic of high public health importance, although the association is not significant. A longer follow-up, cohort study would be necessary to clarify as to whether the correction of the sleep-wake cycle and circadian rhythm by agomelatine would be effective in reducing the usage of the sedative-hypnotics for the depressive patients who use agomelatine.

Furthermore, since several studies have reported that agomelatine could be a novel therapeutic approach for disorders other than MDD, such as irritable bowel syndrome[52] and epilepsy,[53] agomelatine could be suitable for patients with prominent sleep difficulties, or insomnia, for patients with these comorbidities. However, patients using agomelatine require regular liver function checks for the possible hepatotoxic effects.[52,54] In addition, several other side effects, such as dizziness,[55] also require the clinicians' attention and management.

Strengths of This Study

This study has several strengths. First, the present study has been examined from Taiwan's NHIRD, which is a valuable resource to cover a nationwide population, to

Table 5 Comparing the Relative Risk of Hypnotics Between Agomelatine Only and Other Antidepressants

DDD	Antidepressants Subgroup	Populations	Hypnotics		Agomelatine Only vs Other Antidepressants (Reference)			
		n	n	%	Adjusted RR	95% CI	95% CI	*P*
Overall	Agomelatine only	1985	811	40.86				
	Other Antidepressants, Overall	5976	2511	42.02	0.910	0.312	1.633	0.523
	TCA	2012	798	39.66	0.857	0.294	1.394	0.493
	SSRI	2352	896	38.10	0.816	0.281	1.276	0.474
	SNRI	2111	765	36.24	0.782	0.262	1.212	0.453
	NDRI	1986	872	43.91	0.953	0.326	1.489	0.539
	RIMA	2028	803	39.60	0.857	0.293	1.335	0.501
1–29	Agomelatine only	862	366	42.46				
	Other Antidepressants, Overall	2233	901	40.35	0.840	0.289	1.319	0.483
	TCA	990	355	35.86	0.747	0.254	1.167	0.424
	SSRI	1024	429	41.89	0.872	0.297	1.365	0.505
	SNRI	986	376	38.13	0.793	0.264	1.239	0.455
	NDRI	971	425	43.77	0.913	0.308	1.413	0.523
	RIMA	1011	390	38.58	0.801	0.276	1.250	0.463
≧30	Agomelatine only	1123	445	39.63				
	Other Antidepressants, Overall	3743	1610	43.01	0.959	0.328	1.492	0.552
	TCA	1022	443	43.35	0.963	0.321	1.518	0.561
	SSRI	1328	467	35.17	0.788	0.265	1.235	0.453
	SNRI	1125	389	34.58	0.764	0.263	1.213	0.442
	NDRI	1015	447	44.04	0.972	0.341	1.530	0.567
	RIMA	1017	413	40.61	0.915	0.308	1.425	0.520

Abbreviations: DDD, days of drugs used; RR, relative risk; CI, confidence interval; Adjusted RR, adjusted variables listed in Table 2; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; NDRI, norepinephrine dopamine reuptake inhibitor; RIMA, reversible monoamine oxidase inhibitor.

address this issue. Second, several previous studies have demonstrated the accuracy and validity of several diagnoses of neuro-psychiatric disorders in the NHIRD, such as Tourette syndrome,[56] stroke,[57–60] and sleep apnea.[61] Furthermore, studies have also depicted the concordance between Taiwan's National Health Survey and the NHIRD on a variety of diagnoses,[62] medication usage,[62] and health system utilizations.[62,63]

Limitations

This study has several limitations. First, the records of the usage of agomelatine, other antidepressants, and the sedative-hypnotics were recorded in the NHIRD. However, the usage of these medications was assessed based on the prescription records, but the medication compliance and the rate of refills were unknown. Second, diagnoses of the MDD were identified by the ICD-9-CM codes, and the coding errors could be a problem of the NHIRD; therefore, misclassification bias might be an issue. However, large data sets could potentially overcome this problem.[24] In addition, as aforementioned, the verification of in-hospital licensed medical record technician and audit from the NHI Administration would have ensured the accuracy of the data coding process. Third, several important unmeasured confounding factors may have affected the results. For example, the lifestyle of the patients taking antidepressants such as drinking coffee or napping routines was not able to be assessed by the NHIRD. Fourth, similar to previous studies using the NHIRD, the severity, laboratory parameters, genetic, psychosocial, and environmental factors, were not included in the database. Fifth, in this study, the enrolled MDD subjects, with the treatment of agomelatine and other antidepressants, were not stratified by multiple disorders in this database. This is a limitation since anxiety and pain disorders might influence the prevalence of sleep disturbances and the usage of sedative-hypnotic medications in these MDD patients. Sixth, several clinicians would prescribe low dose antidepressants as a sedative-hypnotic medication. However, in this study, the usage of the antidepressants as sedative-hypnotic medications was not analyzed. Seventh, we used 30 days as a cut-off for comparison since the acute phase

treatment is 30 days of treatment duration. Nonetheless, agomelatine had slightly higher response rates as 1.08 (95% CI: 1.02–1.15) when compared to the selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors in the acute phase,[64] and this could be a limitation. Finally, further verification of the generalizability of our results to other countries is therefore needed.

Conclusion

Patients with the agomelatine-only group were not associated with more usage of the sedative-hypnotics than that in the other antidepressant-group. The risk of the usage of sedative-hypnotics was associated with more comorbidities, higher medical care levels, the autumn season of the medical help-seeking, and the subjects living in urban areas. A longer follow-up study would be necessary to clarify as to whether the agomelatine usage is related to the decreased amount of usage of the sedative-hypnotics.

Data Sharing Statement

Data are available from the National Health Insurance Research Database (NHIRD) published by the Taiwan National Health Insurance (NHI) Administration. Due to legal restrictions imposed by the government of Taiwan in relation to the "Personal Information Protection Act", data cannot be made publicly available. Requests for data can be sent as a formal proposal to the NHIRD (http://www.mohw.gov.tw/cht/DOS/DM1.aspx?f_list_no=812).

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. In addition, C-H Chung and W-C Chien conducted the data extraction process and the data were cross-checked by S-C Hsing and N-S Tzeng.

Disclosure

The authors declare that the research was conducted in the absence of any commercial, financial, and non-financial relationships that could be construed as a potential conflict of interest.

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