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ANALYSIS OF AGOMELATINE TREATMENT WITH DEPRESSIVE SYMPTOMS

LING-YU LU*, CHUN-CHIA TSAI

Department of Pharmacy, Taoyuan Psychiatric Center, Taoyuan, Taiwan. Email: lucylu1008@gmail.com

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ABSTRACT

Objective: Agomelatine is a new mechanism of antidepressants, which is approved by Taiwan Food and Drug Administration and available in Taiwan. Agomelatine behaves both as a potent agonist at melatonin MT1 and MT2 receptors and as a neutral antagonist at 5-HT2C receptors. The structures of agomelatine are similar to melatonin with not only the effects to maintain depression symptoms but also can help patients who have insomnia.

Methods: This is a retrospective study. In a mental hospital in Taoyuan, we analyzed the prescriptions of the outpatients who were prescribed agomelatine to realize the effects of agomelatine and whether the prescriptions were prescribed appropriately.

Results: Catastrophic illnesses were found to be associated with significantly used multiple hypnotics (χ^2 =22.02, p<0.001). When patients' age increased by 1 year, multiple hypnotics used increased by 1.013 times (Exp(B)=1.013, p<0.01). Catastrophic illnesses were found to be associated with significantly used augmentation with other antidepressants (χ^2=54.07, p<0.001).

Conclusions: Doctors should be evaluating the benefits and risks when they prescribe a medicine to patients, and they should be written in medical record. This study is the hope to provide relevant units as a reference for formulating health policies.

Keywords: Agomelatine, Melatonin, Insomnia, Chi-squared test, Logistic regression.

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INTRODUCTION

Major depressive disorder (MDD) is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults [1]. Depression and anxiety disorders are commonly comorbid with each other, with estimates of current and lifetime comorbidity often among the highest of any disorders [2]. Although sleep disturbance is a criterion for depression, insomnia is also increasingly being conceptualized as a mechanism in depression etiology [2].

In February 2009, the European Medicine Agency approved agomelatine, a sleep modulating antidepressant, for the treatment of MDD. In adults, it is awaiting approval from the Federal Drug Administration in the USA [3]. Agomelatine is the first approved antidepressant that mediates its activity through the melatoninergic pathway rather than the monoaminergic system [3]. It was approved by Taiwan Food and Drug Administration and available in Taiwan from July 2011.

Agomelatine is an agonist at both melatoninergic MT1 and MT2 receptors; it also has an affinity for 5-HT2C receptor, but it is unlikely that antidepressants effects are mediated through these receptors [4,5]. Agomelatine is a highly accepted antidepressant drug, but there is no definite conclusion about the exact effect of the system [1,6].

The indication for agomelatine is MDD in adults. The initial dose is recommended to be used at bedtime of 25 mg/day. If there is no effect after 2 weeks of treatment, increasing to 50 mg before bedtime is considered [7].

In the Sidney study, [6] in total, 633 patients (422 on agomelatine; 211 on placebo) were included in the analysis. At endpoint, there was a significant difference in favor of agomelatine versus placebo of 3.47 (0.62) (95% confidence interval: [2.26; 4.67]; p<0.001) on the SDS total score. This study confirms the efficacy of agomelatine in improving social functioning in MDD patients.

When using antidepressants, liver function injury should be monitored. A retrospective study by Freiesleben [7] showed that the incidence of liver toxicity caused by agomelatine compared to placebo was 4.6% and 2.1%; the incidence of hepatotoxicity with some other antidepressant drugs is escitalopram 1.4%, paroxetine 0.6%, fluoxetine 0.4%, and sertraline 0%. A retrospective study by Voican *et al*. [8] has showed that hepatotoxicity was caused by six antidepressant drugs, although only 0.5–5% of patients will have mild hepatotoxicity, liver damage is usually unpredictable and most of them occur in elderly people with multiple medications. Therefore, before increasing the dosage and using this medicine, patient's benefits and risks should be evaluated.

Agomelatine has been used in MDD since December 2015. It is a new mechanism of antidepressants in Taiwan. Through its mechanism, agomelatine might be a better choice for people who have both insomnia and depressive disorder.

METHODS

Study design

For this retrospective study of all outpatients who used agomelatine at one psychiatric hospital, Taoyuan Psychiatric Center (TYPC), we collected patient data from the hospital's electronic medical information system from January to December in 2017. The system's electronic medical information system was established in January 2000 and the diagnostic system we used is International Classification of Disease, Tenth, Clinical Modification (ICD-10-CM).

Study sample

This study was conducted at TYPC, a public, regional teaching hospital in North Taiwan. The facility has 282 acute beds, 380 chronic beds, and 300 daycare beds, which treats an average of 1100 patient visits per month and has 30 daycare beds and 30 acute care beds. The protocol for this study was approved by local institutional review board (IRB number: C20180730). Need for informed consent

was waived due to the retrospective nature of the study and ensured patient anonymity.

Research instrument, study variables, and data extraction

Data from the electronic medical information system of the study hospital are transformed into a relational database, referred to as the data "warehouse."

We extracted study data from the warehouse and created our analytic data set using Social Sciences software version 22.0 for Windows (SPSS, Inc., Chicago, Illinois, USA). By reviewing the electronic medical information system, we extracted patients' demographic data such as sex, age, insurance status, psychiatric diagnosis, and prescriptions for patients who were prescribed agomelatine.

The insurance status was divided into patients diagnosed with catastrophic illnesses and those without. The catastrophic illnesses in this study included bipolar disorder, current episode depressed, mild (ICD-10-CM:F31.31), MDD, recurrent severe without psychotic features (ICD-10-CM:F33.2), schizoaffective disorder, and depressive type (ICD-10-CM:F25.1).

Statistical analysis

Categorical variables were compared using Chi-square and Fisher's exact tests, and continuous variables were compared using independent t-tests. Cochran-Armitage trend tests were performed to examine the time trends in the prescriptions of agomelatine and were estimated by multiple logistic regression analysis. We included all of the covariates in the multivariable logistic regression model, including age, gender, with or without catastrophic illnesses, and psychiatric diagnosis. All results were expressed as means and standard deviations.

All statistical analyses were performed using Statistical Package for the Social Sciences software version 22.0 for Windows (SPSS, Inc., Chicago, Illinois, USA). Group differences were considered significant if $p < 0.05$ was considered.

RESULTS

Table 1 shows the analysis of this study, 343 patients were included in this study. Females were 220 (64.14%); males were 123 (35.86%). Agomelatine was prescribed in 1760 visits. As shown in Table 2 (χ^2=1.38, p=0.23), a comparison between genders, there is no significant difference in gender used agomelatine.

The distribution of age is mainly 40–49 years old (30%), the average is 49.97±15.83 years old; the range of age is from 10 to 92. The regression model p=0.630, we can presume that there is no difference in the way of taking agomelatine in different ages.

The diagnosis of those prescriptions of persistent depressive disorder (dysthymia) is part of a cluster of diagnoses called the depressive disorders (ICD-10-CM: F34.1) (14.2%) followed by other depressive episodes (ICD-10-CM: F32.8) (7.2%). In patients' health insurance, catastrophic illnesses were 463 (26.1%), without catastrophic illnesses were 1297 (73.69%). As shown in Table 3 (χ^2=0.17, p=0.67), a comparison between health insurance, there is no significant difference in the way of taking agomelatine in health insurance.

Evaluation of the appropriateness of prescriptions

From January to December 2017, doctors prescribed 1760 prescriptions of agomelatine in outpatients. About 99.6% of frequency was accordance with the recommended use method of agomelatine; 7 were taken at non-bedtime, 5 to be used as needed. All patients took agomelatine due to depressive disorder. The dosage is mainly from 12.25 mg to 50 mg/day, which are all used in appropriate dosage. 25 mg of agomelatine is the most frequently used dosage (59.14%) in a day; in 1760 prescriptions, 76.02% were combined with hypnotics.

In Table 4, hypnotics were prescribed 1753 times, and there were 285 prescriptions containing two kinds of hypnotics. Among the prescriptions, short-acting zolpidem had the highest prescription rate (28.29%) followed by flurazepam (25.90%).

Regarding insurance status, prescriptions contained both agomelatine and hypnotics, catastrophic illnesses are 389 (22.10%), and without catastrophic illnesses are 949 (53.92%). As shown in Table 3 (χ^2 =22.02, p<0.001), catastrophic illnesses were found to be associated with significantly used multiple hypnotics. Age was also found to be associated with significantly used multiple hypnotics, and statistics indicates that when patients' age increased by 1 year, multiple hypnotics used increased by 1.013 times (In Table 5, Exp(B)=1.013, p<0.01).

Table 1: Baseline characteristics of patients

Characteristics	n	%
Age (years)		
<18	3	0.86
19	4	1.17
20~29	32	9.33
30~39	44	12.83
40~49	90	26.24
50~59	76	22.16
60~69	56	16.33
70~74	15	4.37
75~79	11	3.21
80~89	11	3.21
90~99	1	0.29
Gender		
Male	123	35.86
Female	220	64.14
Insurance status		
Non-catastrophic illnesses	1297	73.69
Catastrophic illnesses	463	26.31
Dosage		
12.5 mg	37	2.10
25 mg	1041	59.15
37.5 mg	7	0.40
50 mg	675	38.35
ICD-10-CM diagnosis		
Dysthymic disorder	251	14.29
Other depressive episodes	128	7.29
Adjustment disorder with mixed anxiety and depressed mood	103	5.83
Major depressive disorder, recurrent, moderate	103	5.83
Major depressive disorder, recurrent, unspecified	92	5.25
Major depressive disorder, recurrent severe without psychotic features	87	4.96
Adjustment disorder with depressed mood	77	4.37
Other recurrent depressive disorders	67	3.79
Major depressive disorder, single episode, unspecified	67	3.79
Major depressive disorder, recurrent, severe with psychotic symptoms	67	3.79
Unspecified mood (affective) disorder	62	3.50
Others	657	32.32

Table 2: Comparison between genders

Variables	Gender		χ^2	p value
	Male	Female		
	n	n		
Usage			1.38	0.23
Bedtime	640	1106		
Non-bedtime	3	11		
Polypharmacy			3.72	0.054
No	421	781		
Yes	222	336		

Categorical data were test by χ^2 –test

Table 3: Comparison between health insurance

Variables	Insurance status		χ^2	p value
	Non-catastrophic illnesses	Catastrophic illnesses		
	n	n		
Usage			0.17	0.67
Bedtime	1286	460		
Non-bedtime	11	3		
With hypnotics			22.02	<0.001***
No	348	74		
Yes	949	389		
Polypharmacy			54.07	<0.001***
No	949	253		
Yes	348	210		

Categorical data were test by χ^2 –test, *p<0.05, **p<0.01, ***p<0.001

Table 4: Distribution of hypnotics in prescription

Drug name	Prescription	
	n	(%)
Estazolam	421	24.02
Flurazepam	454	25.90
Zopiclone	207	11.81
Zolpidem	496	28.29
Brotizolam	84	4.79
Triazolam	55	3.14
Zaleplon	36	2.05

Table 5: Correlation between age and multiple hypnotics

Variables	Variables in the equation					
	B	SE	Wald	df	Sig.	Exp(B)
Usage						
Age	−0.009	0.019	0.232	1	0.630	0.991
Constant	−4.388	0.931	22.208	1	0.000	0.012
With hypnotics						
Age	0.013	0.004	11.335	1	<0.01**	1.013
Constant	0.511	0.196	6.770	1	0.009	1.667
Polypharmacy						
Age	−0.005	0.004	1.938	1	0.164	0.995
Constant	−0.525	0.181	8.432	1	0.004	0.592

*p<0.05, **p<0.01, ***p<0.001

Polypharmacy

A total of 558 prescriptions were prescribed for more than 2 kinds of antidepressants, with about 31.70% of patients with augmentation with other antidepressants; 336 were female and 222 were male. As shown in Table 2 (χ^2=3.72, p=0.054), there was no significant difference between gender with augmentation with other antidepressants. Regarding insurance status, prescriptions contained both agomelatine and augmentation with other antidepressants, catastrophic illnesses is 210 (22.10%), and without catastrophic illnesses is 348 (53.92%). As shown in Table 3 (χ^2=54.07, p<0.001), catastrophic illnesses were found to be associated with significantly used augmentation with other antidepressants.

Safety assessment

In 1760 prescriptions of agomelatine, 6 were under the age of 18 (0.34%), the efficacy and safety of agomelatine used in children and adolescents 2–18 years old have not been established, but are still to be used under 18 in some cases in clinical practice. Although there is no significant effect of using agomelatine over 75 years old, 90 prescriptions were prescribed, which was 5.11% of proportion. Three patients had liver injuries (0.17%), but liver function data did not exceed 3 times than normal.

DISCUSSION

To the best of our knowledge, this is the first study to focus on outpatients who used agomelatine to treat depressive disorder in psychiatric hospitals in Taiwan.

Agomelatine is an analog of melatonin, which means that it can treat not only depressive disorder but can also treat insomnia. Agomelatine increased slow-wave sleep and improved sleep quality and continuity, with no effect on REM sleep [9,10]. According to the analysis result, it showed patients who took agomelatine still needed hypnotics to solve their sleep problems. Among the hypnotics that had been chosen, zolpidem had the highest prescription rate (28.29%) followed by flurazepam (25.90%). There is no significant effect in insomnia with agomelatine but we should be concerned about patients' tolerance in hypnotics before they use agomelatine.

Our univariate analysis showed that a higher proportion of females received agomelatine than males, though the difference was not significant.

In our data analysis result, although the safety patients under the age of 18 who use agomelatine was not established, it does not mean that agomelatine cannot be used under the age of 18. Doctors should evaluate the benefit when they are prescribing this medicine.

Some previous studies have found that antidepressant agents have the potential to produce idiopathic liver injury [8,11]. In our study result, there is only one case who had liver injury and used agomelatine. This study has some limitations because we included the data from patients in one psychiatric center. Thus, the diagnosis of some medical illnesses may not specifically be showed in patients' medical records. The clinician must be careful to provide ongoing therapy of the underlying depressive disorder and be aware of possible drug discontinuation syndromes should potential hepatotoxicity be suspected [8]. Some patients have potential liver damage factors such as alcoholic abuse disorders, and patients' liver function should be monitored.

CONCLUSIONS AND RECOMMENDATIONS

Doctors should be evaluating the benefits and risks when they prescribe a medicine to patients, and they should be written in medical record.

This study is the hope to provide relevant units as a reference for formulating health policies.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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