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The Risk of Drug Induced Liver Injury in Agomelatine in Taiwan: a population-based retrospective cohort study

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Introduction

Agomelatine is a novel antidepressant and has been associated with drug induced liver injury (DILI).In Taiwan, agomelatine was approved in July 2011and after 7 years of post-marketing surveillance, Taiwan National ADR Reporting Center has received no report related to agomelatine.

Aim

This study aimed to investigate the prescription pattern of agomelatine in Taiwan, physician compliance to liver function test monitoring for patients treated with agomelatine, and the extent of liver toxicity among agomelatine users.

Methods

Patients who have been exposed to agomelatine, mirtazapine (similar mechanism of action) and trazodone (similar adverse effect) since June 2012 were included. Both outpatient and inpatient claims data of included patients were collected, and the date of first exposure of one of the three drugs was defined as the index date. Reimbursement data for laboratory testing and selected ICD-9-CM codes were used as proxy to study the outcome. Descriptive and Cox-regression model were employed in analysis.

Results

The number of prescriptions increased from about 2,000 per month to about 8,000 per month from July 2012 to May 2015, and 90% of these prescriptions were prescribed from clinics. The drug exposure for agomelatine, mirtazapine, and trazodone were 3172.49, 15209.58 and 938.07 person-years respectively, which corresponds to 6.37, 9.32 and 9.81 DILI events per 100 person-years. No statistical significant difference was observed among these groups. However, risk factors associated with DILI include female, late cohort entrance, on hemodialysis, concomitant viral hepatitis and a history of ischemia stroke.
Overall, compliance of baseline liver function testing was low (32.02%, 46.56% and 32.82% for agomelatine, mirtazapine, and trazodone, respectively) and remains low during treatment period.

Conclusions

No obvious DILI risk with agomelatine use was observed in Taiwan population. However, low rate of liver function testing, especially in patient population at risk for DILI, should be noted.

Table 1. Characteristics of Cohort

Characteristics		Agomelatine		Mirtazapine		Trazodone		p-value
Episodes		16,763		84,659		5,653		
Total episode length(person-year)		3172.49		15209.58		938.07		
Average episode length (days, [Q1-Q3])		67.11 [14-72]		63.06 [14-59]		57.90 [7-42]		
Average defined daily dose (unit, [Q1-Q3])		0.99 [1-1]		0.77 [0.5-1]		0.60 [0.5-0.67]		
Age (mean [Q1-Q3])		50.84 [37-63]		53.04 [39-66]		49.53 [37-60]		
Gender								<.0001
Male		5,752	34.31%	36,714	43.37%	3,124	55.26%	
Female		11,003	65.64%	47,887	56.56%	2,522	44.61%	
Unknown		8	0.05%	58	0.07%	7	0.12%	
Cohort Entry Year								<.0001
2012		1,420	8.47%	19,849	23.45%	1,148	20.31%	
2013		5,468	32.62%	27,598	32.60%	2,067	36.56%	
2014		6,238	37.21%	25,408	30.01%	1,649	29.17%	
2015		3,637	21.70%	11,804	13.94%	789	13.96%	
Specialties								<.0001
Psychiatry		15,081	89.97%	58,835	69.50%	2,461	43.53%	
Neurology		900	5.37%	6,659	7.87%	170	3.01%	
Others		782	4.67%	19,165	22.64%	3,022	53.46%	
Concurrent Medications								
Statins		1,568	9.35%	7,763	9.17%	462	8.17%	0.025
Mood stabilizers		715	4.27%	5,030	5.94%	405	7.16%	<.0001
Antipsychotics		4,515	26.93%	26,880	31.75%	1,614	28.55%	<.0001
Liver Function Test								
Pre-test	Done	4,066	32.02%	26,896	46.56%	1,397	32.82%	<.0001
	At risk	12,697		57,763		4,256		
3 week	Done	665	18.82%	3,578	20.19%	167	21.86%	0.1821
	At risk	3,533		17,719		764		
12 week	Done	180	11.79%	1,025	14.47%	42	10.45%	0.0114
	At risk	1,527		7,085		402		
24 week	Done	99	13.77%	573	15.46%	38	14.56%	0.5921
	At risk	719		3,707		261		

Table 2. Cases and Incidence Estimate of DILI among Treatments Groups

Characteristics	Agomelatine		Mirtazapine		Trazodone	
DILI occurrence						
No DILI	16,561	98.79%	83,242	98.33%	5,561	98.37%
DILI	**202**	**1.21%**	**1,417**	**1.67%**	**92**	**1.63%**
Under pre-existing DILI history	97	0.58%	690	0.82%	52	0.92%
DILI occur while treatment on	70	0.42%	399	0.47%	25	0.44%
DILI occur while treatment on and persisted after discontinued	10	0.06%	71	0.08%	4	0.07%
DILI occur at risk window after stop medication	25	0.15%	257	0.30%	11	0.19%
Incidence(cases per 100 person-years)	**6.37**		**9.32**		**9.81**	
ICD-9-CM code						
570,572.2,572.4[Liver necrosis, hepatic coma, hepatorenal syndrome]	17	0.10%	400	0.47%	17	0.30%
572.8,573.(3,8,9)[Hepatitis]	183	1.09%	987	1.17%	75	1.33%
277.4, 50.1, 50.9[Bilirubin disorder, liver biopsy]	2	0.01%	29	0.03%	-	0.00%
V472, 50.59[Liver transplantation]	-	0.00%	1	0.00%	-	0.00%

Table 3. Risk Factors Identified associated with DILI

Variables	OR	95%CI
Medication		
Agomelatine	1.000	
Mirtazapine	1.005	0.854 - 1.184
Trazodone	1.185	0.898 - 1.563
Gender		
Male	1.000	
Female	**1.270**	**1.141 - 1.414**
Cohort Entry Year		
2012	1.000	
2013		0.924 1.217
2014	1.142	0.991 1.317
2015	**1.470**	**1.226 1.763**
Backgroud History		
Hemodialysis	**1.998**	**1.229 - 3.248**
HBV infection	**2.333**	**1.863 - 2.922**
HCV infection	**2.056**	**1.623 - 2.605**
Alcoholic hepatitis	0.545	0.461 - 0.645
Drug induced liver injury	0.086	0.077 - 0.096
Hepatocellular carcinoma	0.313	0.231 - 0.424
Hemorrrahgic stroke	1.011	0.721 - 1.419
Ischemic stroke	**1.307**	**1.062 - 1.608**
Myocardiac ischemia	0.881	0.609 - 1.274

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