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Psychotropic drugs and risk of motor vehicle accidents: a population-based case-control study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- It has long been known that psychotropic drugs impair cognitive and psychomotor abilities.
- Most studies have mainly focused on the relationship between benzodiazepines (BZDs) and motor vehicle accidents (MVAs). Limited information is available regarding an assessment of the effect of the new classes of psychotropic drugs on MVAs.

WHAT THIS STUDY ADDS

- In addition to BZDs (including long acting, short acting, hypnotic and anxiolytic), exposure to antidepressants (SSRIs and TCAs) and Z-drugs was significantly associated with an increased risk of MVAs.
- The findings underscore that subjects taking these psychotropic medications should pay increased attention to their driving performance in order to prevent the occurrence of MVAs.

AIM

To examine comprehensively the relationship between exposure to four classes of psychotropic drugs including antipsychotics, antidepressants, benzodiazepines (BZDs) and Z-drugs, and motor vehicle accidents (MVAs).

METHOD

The authors conducted a matched case-control study of 5183 subjects with MVAs and 31 093 matched controls, identified from the claims records of outpatient service visits during the period from 2000 to 2009. Inclusion criteria were defined as subjects aged equal to or more than 18 years and involved in MVAs. Conditional logistic regressions with covariates adjustment (including urbanity, psychiatric and non-psychiatric outpatient visits and Charlson comorbidity score) were applied to examine the effect of four classes of psychotropic drugs on MVAs.

RESULTS

Significant increased risk of MVAs was found in subjects taking antidepressants within 1 month (adjusted odds ratio (AOR) 1.73, 95% confidence interval (CI) 1.34, 2.22), 1 week (AOR 1.71, 95% CI 1.29, 2.26), and 1 day (AOR 1.70, 95% CI 1.26, 2.29) before MVAs occurred. Similar results were observed in subjects taking benzodiazepines (BZDs) (AOR 1.56, 95% CI 1.38, 1.75 for 1 month; AOR 1.64, 95% CI 1.43, 1.88 for 1 week, and AOR 1.62, 95% CI 1.39, 1.88 for 1 day) and Z-drugs (AOR 1.42, 95% CI 1.14, 1.76 for 1 month, AOR 1.37, 95% CI 1.06, 1.75 for 1 week, AOR 1.34, 95% CI 1.03, 1.75 for 1 day), but not antipsychotics. Moreover, significant dose effects of antidepressants (equal to or more than 0.6–1.0 DDD), BZDs (equal to or more than 0.1–0.5 DDD) and Z-drugs (more than 1 DDD) were observed, respectively, on the risk of experiencing an MVA.

CONCLUSION

Taken together, subjects taking antidepressants, BZDs and Z-drugs, separately, should be particularly cautioned for their increasing risk of MVAs.

Introduction

Road traffic accidents are one of the leading causes of death by injury and are projected to be the third leading cause of disease burden globally by 2020 [1]. In Taiwan, according to the report by the Department of Health, accidents have been ranked fifth among the 10 most common causes of death in recent years, of which more than 90% are attributed to motor vehicle accidents (MVAs) [2]. Based on the MVA statistics, there were 184 749 MVAs in Taiwan in 2009, resulting in a considerable casualty toll of 2092 dead, and 246 959 injured [3].

It has been long known that psychotropic drugs impair cognitive and psychomotor abilities, which are crucial for manoeuvering vehicles to a significant extent, thus conferring a high risk of MVAs [4, 5]. Such an effect has been particularly prominent with benzodiazepines (BZDs) [6–14], antidepressants [15–18], antipsychotics [19–21], zolpidems and their related agents [8, 22]. With the majority of drug-related MVA studies focusing on BZD use [6–15, 22–24], some groups have reported that anxiolytic BZDs were more risky than hypnotic BZDs [20]. Others suggested that long acting BZDs triggered more frequent MVAs, particularly in the elderly and in contrast to short-acting BZDs [25, 26].

Currently, most studies have mainly focused on the relationship between BZDs and MVAs. Despite the number of newer psychotropic drugs (i.e. selective serotonin re-uptake inhibitors (SSRIs) and atypical antipsychotics) that have been launched during the past few years, limited information is available regarding the assessment of the effects of these newer classes of psychotropic drugs on MVAs [5]. The objectives of this study were (i) to provide comprehensive and new insightful information on the effect of a wide spectrum of psychotropic drugs, including the newer classes of psychotropic drugs, on MVAs, which has barely been addressed among Asians in a single study and (ii) to explore further the dose–response effect of psychotropic drugs on MVAs.

Methods

Data sources

In this study, data were obtained from the National Health Insurance Research Database (NHIRD) in Taiwan, which are derived from the National Health Insurance (NHI) programme. In detail, the NHI programme provides comprehensive, unified and universal medical care services for more than 99% of the total population in Taiwan. The large computerized datasets derived from the NHI programme contain registry and claims data such as outpatient services, inpatient care, dental care, physical therapy, preventive health care, home care and rehabilitation for chronic mental illness. The registry and claims data were collected by the Bureau of National Health Insurance and maintained at the National Health Research Institutes (NHRI) in Taiwan. Data from the NHIRD are available to investigators for research purposes. This study utilized one of the data subsets in the NHIRD gathered from 2000 to 2009. Specifically, the subset, the Longitudinal Health Insurance Database 2000 (LHID2000), contains all original claims data from 1 000 000 individuals (roughly 5% of the total population) randomly sampled from the NHIRD. Detailed information on the sampling method representative of the LHID2000 is provided at the following link: (http://w3.nhri.org.tw/nhird/date_cohort.htm#2) [27]. For each NHI beneficiary, a unique encrypted identification number was used to retrieve medical claims data for inpatient and ambulatory care services. This study protocol was approved by the Institutional Review Board at the National Health Research Institutes.

Definition of cases with motor vehicle accidents

Eligible cases included subjects aged equal to or more than 18 years with the diagnosis of motor vehicle accidents (MVAs) (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code = E810-825). We excluded subjects (both cases and controls) involved in vehicle accidents coding with fifth digit subdivisions of .1, .3, .4, .5 and .7, which indicated that the involved vehicle accidents were non-driver accidents [28], from January 1 2000 to December 31 2009 in the outpatient claims. The date of the first outpatient MVA claim was defined as the index date.

Definition of the comparison group

The inclusion criteria of the comparison group were as follows: (i) subjects were randomly drawn from those who did not have any outpatient record for MVA- associated visits and (ii) subjects were individually matched with cases by age, gender and the year of vehicle accidents in a 1:6 ratio. In detail, the matching process included the following three steps: (i) generating a randomized list of the controls who were of the same birth year gender and same year of vehicle accident as the matched MVA case, (ii) selecting the first six controls from the randomized list of those who had not yet been selected as matched controls and (iii) repeating steps 1 and 2 for the next MVA case. If there were less than six eligible controls, then all controls were selected. We excluded subjects under age 18 years. Additionally, in order to make medication exposure and MVA risks comparable over the same period of time, each comparison subject was assigned an index date matching the MVA case, which was the same index date as for the matched MVA case.

Definition of psychotropic drug utilization

The utilization of psychotropic drugs was based on prescriptions recorded in the LHID2000 from 2000 to 2009. All

subjects were considered to have exposure to psychotropic drugs if any of their psychotropic prescription dates overlapped with the index date. The categories of psychotropic drugs examined in this study were determined on the basis of codes in the Anatomical Therapeutic Chemical (ATC) classification system as follows:

(1) Antipsychotics (ATC code: N05A). We classified antipsychotic medications into two groups: (i) typical antipsychotic – chlorprothixene, chlorpromazine, chlorprothixene, clopenthixol, clothiapine, droperidol, flupentixol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, sulpiride, thioridazine, thiothixene and trifluoperazine and (ii) atypical antipsychotic (ATC code: N05X) – amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone and zotepine. (2) Antidepressants. Antidepressants were classified into the following three groups: (i) SSRI (selective serotonin reuptake inhibitor; ATC code: N06AB) – fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram and escitalopram, (ii) TCA (tricyclic antidepressants; ATC code: N06AA) – imipramine, amitriptyline, maprotiline, doxepin, clomipramine and dothiepin and (iii) other antidepressants (ATC codes: N06AF, N06AG and N06 AX) – bupropion, venlafaxine, duloxetine, mirtazapine and moclobemide. (3) Benzodiazepines (BZDs). BZDs were grouped into (i) hypnotics (ATC code: N05C) – triazolam, midazolam, temazepam, estazolam, flurazepam, flunitrazpam and lormetazepam and (ii) anxiolytics (ATC code: N05B) – alprazolam, bromazepam, brotizolam, chlordiazeproxide, clobazam, clonazepam, clorazepate, cloxazolam, nitrazepam, nordazepam, oxazepam, oxazolam, diazepam, fludiazepam, lorazepam, medazepam and nimetazepam. In addition, BZDs were also categorized into long acting (half-life >24 h), including diazepam, flurazepam, chlordiazepoxide and clonazepam and short acting (<24 h), including all other BZDs listed above. (4) Z-drugs (ATC code: N05CF): zolpidem, zolpiclone and zaleplon.

We further categorized the status of psychotropic use based on the prescription date plus the duration of drug supply. Psychotropic exposure was classified as psychotropic users, defined as having a prescribed claims record of psychotropic drug supply within 1 day, 1 week or 1 month prior to the index date or non- psychotropic users, defined as not having any prescribed claims record of psychotropic drug supply within 1 day, 1 week or 1 month prior to the index date. Of note, the prescribed claims record was included if the claim date was the same as the index date.

Using the ATC classification system, we calculated the defined daily dose (DDD) of the psychotropic prescriptions that overlapped with the index date, based on the prescription date, medication dosage and the duration of drug supply [29]. According to the distribution of the doses, subjects were divided into the following four groups: no use, 0.1–0.5 DDD, 0.6–1.0 DDD and >1.0 DDD.

Covariates

It has been previously reported that medical and mental conditions and health care utilizations are important risk factors contributing to automobile crashes [11, 30]. Therefore, we extracted the data of the Charlson comorbidity score (CCS), a prospectively applicable method derived from converting diagnosis codes into 19 clinical conditions to classify comorbid conditions which might alter the risk of mortality [31], and psychiatric and non-psychiatric outpatient visits within 180 days of MVAs as indicators from the NHIRD to account for the physical and mental states of the study samples. In addition, a previous study has reported the inverse correlation between mortality from motor vehicle crashes and urbanization [32]. Therefore, we also included urbanity as a covariate in all analytical models. In particular, we grouped subjects who visited psychiatrists as psychiatric outpatient visits, and all other visits as non-psychiatric outpatient visits.

Statistical analyses

A chi-square test was used to compare demographic characteristics, such as urbanity (urban, suburban and rural) and health care utilization (psychiatric and non-psychiatric outpatient visits) between MVA cases and subjects in the comparison group. Student's *t*-test was applied to examine the difference in physical condition (using CCS as a proxy) between MVA cases and subjects in the comparison group. In the subsequent analyses, the dependent variable was MVA and the independent variables were urbanity, psychiatric and non-psychiatric outpatient visits and CCS. The not exposed group was defined as subjects without taking any of the examined psychotropic drugs within the three examined periods (1 day, 1 week or 1 month prior to the index date) and the exposed group was defined as subjects taking at least one class of the examined psychotropic drugs within one of the three examined periods. We applied conditional logistic regression to examine the effect of various kinds of psychotropic drugs (i.e. antipsychotics, antidepressants, BZDs and Z-drugs) and their corresponding sub-groups on MVAs with and without covariate adjustment, and performed the analyses separately for subjects taking psychotropic drugs at different time periods (within 1 month, 1 week and 1 day). Likewise, the dose effect of psychotropic drugs on the risk of MVAs was tested using conditional logistic regression with and without covariate adjustment. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated to determine whether the findings were statistically significant. Data analyses in this study were carried out using the statistical package R 2.10.0 (http://www.r-project.org) and SAS software (version 9.2; SAS Institute, Inc., Cary, North Carolina, USA), respectively.

Results

A total of 36 276 subjects (5183 cases and 31 093 comparison subjects) were included in the study. Demographic characteristics of MVA cases and matched controls are presented in Table 1. Generally, the study sample included more males than females (53.4% males and 46.6% females). The mean and the corresponding standard deviation (SD) of age were 38.4 ± 17.4 years in the study sample, with 30.4% aged less than 25 years, 35.5% aged between 25 and 44 years, 23.3% aged between 45 and 64 years and 10.8% aged equal to or more than 65 years. MVA cases tended to live in suburban areas ($\chi^2 = 131.36$, $P < 0.0001$), had more psychiatric outpatient visits ($\chi^2 = 18.57$, $P < 0.0001$), had more non-psychiatric outpatient visits ($\chi^2 = 647.50$, $P < 0.0001$) and had higher CCS ($t = -4.57$, $P < 0.0001$) than matched controls.

The descriptive data in Table 2 presents the numbers and corresponding percentages of MVA cases and matched controls who took various classes of psychotropic drugs (i.e. antidepressants, antipsychotics, BZDs, and Z-drugs) and were grouped by different medication lengths (within 1 month, 1 week and 1 day, separately) before MVAs occurred. In general, the percentage of those taking different classes of psychotropic drugs in the MVA cases was higher than for those in the matched controls.

Table 3 shows the associations between various classes of psychotropic drugs and MVAs, grouped by different medication lengths (within 1 month, 1 week and 1 day,) before MVAs occurred. A significantly increasing risk of MVAs was observed among subjects taking antidepressants within 1 month before MVAs occurred (adjusted odds ratio (AOR) 1.73, 95% CI 1.34, 2.22), after adjusting for urbanity, psychiatric outpatient visits and CCS, respectively. Similar patterns also were observed for subjects taking antidepressants within 1 week (AOR 1.71, 95% CI 1.29, 2.26) and/or 1 day (AOR 1.70, 95% CI 1.26, 2.29) before MVAs occurred. When we further stratified antidepressants by SSRIs and TCAs, the increased risk of MVAs was observed among subjects taking SSRIs or TCAs within 1 month, 1 week and/or 1 day, separately, before MVAs occurred (Table 3). While examining the effect of antipsychotic use (both typical and atypical) on MVAs, our results showed no significant associations between exposure to antipsychotics (within 1 month, 1 week or 1 day) and MVAs.

In terms of BZD use, a significantly increasing risk of MVAs was found among subjects taking BZDs within 1 month before MVAs (AOR 1.56, 95% CI 1.38, 1.75), after adjusting for urbanity, psychiatric outpatient visits and CCS, separately. Similar results were observed for subjects taking BZDs within 1 week (AOR 1.64; 95% CI 1.43, 1.88), and 1 day (AOR 1.62, 95% CI 1.39, 1.88), before MVAs

Table 1

Demographic characteristics in MVA cases and matched controls

	Case (n = 5183)	%	Control (n = 31 093)	%	Chi-square	P
Age (years)						
<25	1,573	30.4	9,438	30.4	NA†	
25–44	1,842	35.5	11,052	35.5		
45–64	1,206	23.3	7,236	23.3		
≥65	562	10.8	3,367	10.8		
Gender						
Female	2,413	46.6	14,478	46.6	NA	
Male	2,770	53.4	16,615	53.4		
Psychiatric outpatient visits within halfa year before MVAs						
No	5,036	97.2	30,499	98.1	18.57	<0.0001
Yes	147	2.8	594	1.9		
Non-psychiatric outpatient visits within half a year before MVAs						
No	0	0.0	3,515	11.3	647.50	<0.0001
Yes	5,183	100.0	27,578	88.7		
Urbanity						
Urban	1,204	23.2	9,357	30.1	131.36	<0.0001
Suburban	3,366	64.9	19,051	61.3		
Rural	613	11.8	2,685	8.6		
	Mean	**SD‡**	**Mean**	**SD**	**t test**	**P**
Charlson comorbidity score	0.6	1.3	0.5	1.2	–4.57	<0.0001
Age (years)	38.4	17.4	38.4	17.4	–0.04	0.9716

MVA: motor vehicle accident. †NA: not applicable; since cases were matched with controls by age, gender and the year of vehicle accidents. ‡SD: standard deviation.

Table 2

The numbers and percentages of MVA cases and matched controls regarding various classes of psychotropic drug use, grouped by different lengths of use before MVAs occurred (within 1 month, 1 week and 1 day)

	1 month				1 week				1 day			
	Case		Control		Case		Control		Case		Control	
	n = 5183	%	*n* = 31 093	%	*n* = 5183	%	*n* = 31093	%	*n* = 5183	%	*n* = 31 093	%
Antidepressants	107	2.1	325	1.1	81	1.6	240	0.8	72	1.4	212	0.7
SSRI	52	1.0	146	0.5	43	0.8	113	0.4	38	0.7	101	0.3
TCA	49	1.0	143	0.5	35	0.7	93	0.3	30	0.6	81	0.3
Others	14	0.3	53	0.2	7	0.1	41	0.1	7	0.1	35	0.1
Antipsychotics	84	1.6	364	1.2	63	1.2	255	0.8	56	1.1	226	0.7
Atypical	17	0.3	77	0.3	14	0.3	60	0.2	14	0.3	59	0.2
Typical	72	1.4	294	1.0	53	1.0	197	0.6	46	0.9	169	0.5
BZDs	471	9.1	1,804	5.8	342	6.6	1,213	3.9	282	5.4	995	3.2
Half-life												
Long acting	164	3.2	527	1.7	108	2.1	308	1.0	82	1.6	225	0.7
Short acting	380	7.3	1,424	4.6	279	5.4	978	3.2	232	4.5	822	2.6
Subgroup												
Anxiolytics	437	8.4	1,631	5.3	312	6.0	1,068	3.4	250	4.8	869	2.8
Hypnotics	98	1.9	330	1.1	73	1.4	254	0.8	70	1.4	224	0.7
Z-drugs	117	2.3	438	1.4	87	1.7	329	1.1	78	1.5	297	1.0

MVA: motor vehicle accident.

Table 3

Association between various classes of psychotropic drug use and MVA, grouped by different lengths of use before MVAs occurred (within 1 month, 1 week and 1 day)

	1 month				1 week				1 day			
	OR†	95% CI†	AOR§,¶	95% CI	OR	95% CI	AOR	95% CI	OR	95% CI	AOR	95% CI
Antidepressants	**2.01**‡	1.61,2.51	**1.73**	1.34,2.22	**2.05**	1.59,2.64	**1.71**	1.29,2.26	**2.06**	1.57,2.70	**1.70**	1.26,2.29
SSRI	**2.16**	1.57,2.97	**1.72**	1.20,2.47	**2.29**	1.61,3.25	**1.80**	1.22,2.65	**2.26**	1.56,3.29	**1.74**	1.15,2.63
TCA	**2.09**	1.50,2.90	**1.77**	1.27,2.48	**2.28**	1.54,3.37	**1.93**	1.29,2.87	**2.24**	1.47,3.42	**1.88**	1.23,2.90
Others	1.59	0.88,2.86	1.17	0.64,2.15	1.03	0.46,2.28	0.74	0.33,1.69	1.20	0.53,2.70	0.86	0.38,1.98
Antipsychotics	**1.39**	1.10,1.77	1.09	0.83,1.43	**1.49**	1.13,1.97	1.14	0.83,1.55	**1.50**	1.11,2.01	1.11	0.80,1.54
Atypical	1.33	0.78,2.25	0.91	0.52,1.59	1.40	0.78,2.51	0.97	0.53,1.78	1.43	0.80,2.56	0.96	0.52,1.77
Typical	**1.48**	1.14,1.92	1.19	0.90,1.58	**1.62**	1.20,2.20	1.27	0.91,1.77	**1.64**	1.18,2.28	1.26	0.89,1.80
BZDs	**1.68**	1.50,1.88	**1.56**	1.38,1.75	**1.79**	1.58,2.04	**1.64**	1.43,1.88	**1.78**	1.55,2.05	**1.62**	1.39,1.88
Half-life												
Long acting	**1.91**	1.60,2.29	**1.72**	1.43,2.07	**2.15**	1.72,2.68	**1.89**	1.50,2.38	**2.22**	1.72,2.87	**1.91**	1.47,2.49
Short acting	**1.70**	1.51,1.92	**1.56**	1.37,1.78	**1.79**	1.56,2.06	**1.63**	1.40,1.89	**1.76**	1.51,2.05	**1.59**	1.35,1.87
Subgroup												
Anxiolytics	**1.73**	1.54,1.93	**1.60**	1.41,1.80	**1.86**	1.63,2.13	**1.70**	1.47,1.96	**1.81**	1.56,2.09	**1.63**	1.40,1.91
Hypnotics	**1.80**	1.43,2.26	**1.51**	1.19,1.94	**1.74**	1.34,2.26	**1.44**	1.09,1.91	**1.89**	1.44,2.48	**1.56**	1.17,2.08
Z-drugs	**1.63**	1.32,2.01	**1.42**	1.14,1.76	**1.61**	1.26,2.04	**1.37**	1.06,1.75	**1.60**	1.24,2.06	**1.34**	1.03,1.75

MVAs: motor vehicle accidents. †OR: crude odds ratio and corresponding 95% confidence interval (CI).‡Significant results are in bold. §AOR: adjusted odds ratio. ¶Adjusted covariates including urbanity, psychiatric and non-psychiatric outpatient visits and Charlson comorbidity score.

occurred. Interestingly, when we further classified BZDs into long acting *vs.* short acting, or anxiolytics *vs.* hypnotics, the significantly increasing risk of MVAs remained for all three lengths of BZD use (1 month, 1 week and 1 day, individually) (Table 3).

Likewise, a significantly increased risk of MVAs was observed in subjects taking Z-drugs; specifically, the AOR was equal to 1.42 (95% CI 1.14, 1.76) for exposure within 1 month, 1.37 (95% CI 1.06, 1.75) for exposure within 1 week and 1.34 (95% CI 1.03, 1.75) within 1 day, respectively, before MVAs occurred (Table 3).

We further assessed the dose effect of exposure to psychotropic drugs on the risk of experiencing an MVA. Using non-users as the reference group, exposure to antidepressants equal to 0.6–1 DDD or >1 DDD significantly increased the risk of MVAs (AOR 1.63, 95% CI 1.00, 2.65 for the group with 0.6–1 DDD, AOR 2.33, 95% CI 1.42, 3.83 for the group with >1 DDD, respectively). Using non-users as the

Table 4

Dose effect of psychotropic drug use on the index date of MVA

Dosage	Case (n = 5183)	%	Control (n = 31 093)	%	OR‡	95% CI	AOR¶,**	95% CI
Antidepressants								
No use	5,111	98.61	30,881	99.32	1.00		1.00	
0.1–0.5 DDD	22	0.42	83	0.27	**1.62**§	1.01,2.60	1.42	0.88,2.30
0.6–1 DDD	24	0.46	75	0.24	**1.93**	1.22,3.06	**1.63**	1.00,2.65
>1 DDD	26	0.5	54	0.17	**2.90**	1.82,4.63	**2.33**	1.42,3.83
BZDs†								
No use	4,901	94.6	30,098	96.8	1.00		1.00	
0.1–0.5 DDD	89	1.7	401	1.3	**1.40**	1.11,1.77	**1.31**	1.03,1.66
0.6–1 DDD	93	1.8	327	1.1	**1.79**	1.42,2.26	**1.66**	1.30,2.10
>1 DDD	100	1.9	267	0.9	**2.34**	1.85,2.95	**2.09**	1.63,2.68
Antipsychotics								
No use	5,127	98.9	30,870	99.3	1.00		1.00	
0.1–0.5 DDD	36	0.7	134	0.4	**1.62**	1.12,2.35	1.31	0.89,1.93
0.6–1 DDD	9	0.2	42	0.1	1.29	0.63,2.65	0.90	0.43,1.90
>1 DDD	11	0.2	47	0.2	1.41	0.73,2.72	0.92	0.46,1.83
Z-drugs								
No use	5,105	98.5	30,796	99.04	1.00		1.00	
0.1–0.5 DDD	3	0.06	38	0.12	0.48	0.15,1.56	0.42	0.13,1.37
0.6–1 DDD	43	0.83	185	0.59	**1.41**	1.01,1.97	1.20	0.85,1.70
>1 DDD	32	0.62	74	0.24	**2.60**	1.72,3.94	**2.11**	1.38,3.23

MVAs: motor vehicle accidents. †BZDs: benzodiazepines. ‡OR: crude odds ratio and corresponding 95% confidence interval (CI). §Significant results are in bold. ¶AOR: adjusted odds ratio. **Adjusted covariates including urbanity, psychiatric and non-psychiatric outpatient visits and Charlson comorbidity score.

reference group, a significantly increased risk of MVAs was observed (AOR 1.31, 95% CI 1.03, 1.66) even when BZD exposure was at a low dosage (0.1–0.5 DDD). When BZD dose was increased, increased risks were also found (AOR 1.66, 95% CI 1.30, 2.10 in the group taking BZDs = 0.6–1 DDD and AOR 2.09, 95% CI 1.63, 2.68 in the group taking BZDs >1 DDD). Similarly, when users were exposed to Z-drugs >1 DDD, an increased risk of MVAs was observed (Table 4). On the contrary, exposure to antipsychotics did not increase the risk of MVAs, even in the highest dosage group (>1 DDD). Notably, the results of exposure to antidepressants equal to 0.6–1 DDD (AOR 1.63, 95% CI 1.00, 2.65), and exposure to BZDs equal to 0.1–0.5 DDD (AOR 1.31, 95% CI 1.03, 1.66) were found to be of borderline significance. Therefore, caution must be applied when interpreting the study outcomes.

Discussion

While the positive association between BZDs and MVAs has long been known [9, 33], limited studies have comprehensively and simultaneously examined the effect of various classes of psychotropic drugs, including antidepressants, antipsychotics, BZDs and Z-drugs, and MVAs in a single large nationwide population-based study. This study is one of the few studies to investigate simultaneously the respective effects of these various types of psychotropic drugs on the risk of MVAs. Our findings show that exposure to antidepressants (including SSRIs and TCAs), BZDs (including long acting, short acting, hypnotics and anxiolytics) and Z-drugs was significantly associated with an increased risk of MVAs.

In this study, we found that current antidepressant use (both SSRIs and TCAs) was significantly associated with an increased risk of MVAs with medication lengths of 1 month, 1 week and 1 day, before MVAs occurred. These results were consistent with the previous study reported by Ray *et al*. [15] who found an association between TCA use among elderly drivers and an increased risk of MVAs, and Ravera *et al*. [5] recently reported an increased risk of traffic accidents among SSRI drug users. Our findings contrasted those found in a previous study reported by Barbone *et al*. [8] who found that neither SSRI nor TCA use was associated with an increased risk of MVAs. Another previous study found that a higher dosage of antidepressant use impaired driving function [15]. Our results suggest that an antidepressant dosage >0.6 DDD significantly increases the risk of MVAs. Further investigation would be needed to elucidate the inconclusive relationship between antidepressant use and MVAs in different independent study cohorts.

Meanwhile, the effect of BZDs on MVAs has been widely recognized. A previous report found that anxiolytic BZD use increased the risk of MVAs [6]. Some other studies also suggested that long acting BZD use may significantly trigger MVAs, particularly in the elderly [8, 26]. Our results demonstrated that all subtypes of BZD use (including long

acting, short acting, hypnotic and anxiolytic) within the three examined lengths of exposure (1 day, 1 week and 1 month) were significantly associated with an increased risk of MVAs. A relationship between dose–response to BZD exposure and the risk of MVAs was also noted previously [8, 15]. Ray *et al*. [15] reported that high-dose BZDs use, specifically doses of more than 20 mg diazepam, significantly increased the risk of MVAs. Interestingly, our results demonstrated that BZD use increased the risk of MVAs even at a low dose level such as 0.1–0.5 DDD. In addition, previous studies have also reported that current zolpidem use, one kind of Z-drug, increased the risk of MVAs [8, 18]. Similarly, our results showed that taking Z-drugs increased the risk of MVAs. On the other hand, Orriols *et al*. did not find an association between zolpidem use and causation of traffic accidents [34]. As such, the potential risk of zolpidem use on MVAs should be further investigated.

In addition to findings related to MVAs, several studies have reported that the medical treatment of subjects with psychiatric conditions had a positive effect on driving performance and/or driving impairment [19, 35]. For example, Judd has reviewed five MVA related surveys and reported that patients with schizophrenia demonstrated improvement of psychomotor performance during chronic treatment with antipsychotic drugs [19]. On the contrary, it was noted that typical antipsychotics may induce extrapyramidal side effects which may impair driving capability [21]. However, to the best of our knowledge, no previous studies have examined the influence of different kinds of antipsychotics (both typical and atypical) on the risk of MVAs. Our results did not find that exposure to antipsychotics (both typical and atypical) was associated with the risk of MVAs. As such, it would be of interest to explore further the relationship between antipsychotics and MVAs.

Despite previous findings supporting the association between the effect of psychotropic drugs and MVAs, Orriols *et al*. further examined the association between prescription medicines and the risk of road traffic crashes in a French registry-based data study and reported that the use of prescription medicines was associated with a substantial number of road traffic crashes [36]. Hooper *et al*. investigated the association between prescribed medications and fatal motor vehicle crashes (MVC) in a military population over a 5 year study period using available electronic data and found that the association between prescribed antidepressants and fatal MVC may reflect unmeasured co-morbidities [37]. Interestingly, the findings observed in our study were in line with both of these previous reports.

This study has several strengths. First, this study has a large sample size since the study was conducted based on Taiwan's nationwide NHIRD data. Second, most existing literature has only investigated the association between one type of psychotropic drug and MVAs in a single study. This is one of the few studies to examine simultaneously four different types of psychotropic drugs (antidepressants, antipsychotics, BZDs and Z-drugs) in a single study. This facilitated our efforts to investigate comprehensively the potential influences of various kinds of common psychotropic medications on MVAs. Third, the majority of related published studies were performed in Western countries. This is one of the few studies examining the effects of a wide spectrum of psychotropic drugs on MVAs in an Asian population.

On the other hand, caution should be used when interpreting the results derived from this study. First, we may have underestimated the effect of psychotropic drugs on MVAs. For example, based on the MVA statistics provided by the Bureau of Police, Department of Internal Affairs in Taiwan [3], a total of 1 692 856 persons were injured due to MVAs during 2000–2009, compared with 5183 cases investigated in this study. It is likely that subjects with less severe MVAs may have not visited medical care facilities, and as a result, the MVA would not have been collected by NHIRD. Similarly, data from MVAs that resulted in death were not available. Thus, the effects of psychotropic drugs on MVAs that involve death remain unclear. Second, NHIRD only provided information related to the dispensing of psychotropic drugs. Since non-compliance or therapy adherence has been considered a potential confounder, caution should be applied when comparing our findings with the results reported by other groups, in which data were collected from clinical settings [24]. Third, the NHIRD data were originally established and collected for administrative and reimbursement purposes. Although we matched age and gender in this study and further treated urbanity, psychiatric and non-psychiatric outpatient visit and CCS as covariates in the analytical models, it is likely that additional risk factors (i.e. recent relocation, high job stress and prior MVAs, etc.) associated with MVAs should be taken into account, but were not included in this study. Fourth, no information regarding a driver's licence was available in the NHIRD. Study subjects may or may not have held a driver's licence. Therefore we may have underestimated MVA risk, especially in the control group. However, such underestimation of MVA risk should have occurred in both groups. In addition, no data regarding weather conditions and/or time of day were collected in this study, although the influence of the weather should be similar between MVA cases and comparison controls. Fifth, the use of alcohol and/or illicit drugs was not investigated in this study. It would be of interest to examine simultaneously the effects of the use of psychotropic drugs and alcohol/illicit drugs in a single study. Likewise, it would be important to explore differences between cases and controls in relation to driving patterns, driving experience, co-morbidities, risk taking behaviours, weather conditions and vehicle types, etc. Lastly, unlike most previous investigations that focused on driving performance under pharmacologic treatment in hospital-based populations, this study was conducted in a general population [38–40]. In

addition, we did not investigate the role of polypharmacy in this study population. Even though our results support that BZD use is significantly associated with an increased risk of MVAs, similar to previous observations in clinical populations, more investigation in general populations and of the polypharmacy issue would be needed to document the findings from our study.

Importantly, the results of this study confirm previous findings that psychotropic medications increase the risk of MVAs [4, 5]. This study contributes additional evidence to documenting that psychotropic medications can constitute a considerable degree of danger to traffic safety in an Asian population. Furthermore, the convincing evidence from this study highly suggests that drivers taking psychotropic medication should be particularly aware of the risk of MVAs and receive proper counselling from their health care providers.

In conclusion, this study provides compelling evidence that the use of antidepressants (including SSRIs and TCAs), BZDs (including long acting, short acting, hypnotics and anxiolytics) and Z-drugs, individually, is significantly associated with MVAs. These findings underscore that subjects taking psychotropic medications should pay increased attention to their driving performance in order to prevent the occurrence of MVAs. It is of importance that physicians and pharmacists provide their patients with accurate advice, choose safer, alternative treatments and advise patients not to drive, especially while taking medications, to minimize the risk of causing MVAs under the influence of psychotropic medications. In addition, studies to investigate simultaneously the influence of various kinds of psychotropic drugs on MVAs are warranted.

Competing Interests

There are no competing interests to declare.

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