ZOLPIDEM USE AND
RISK OF FATAL MOTOR VEHICLE COLLISIONS

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INTRODUCTION
In a simulation study evaluating the residual effects of taking a single night-time dose of hypnotics among health individuals on collision anticipation capacities in the next morning, investigators found no residual effect by having taken a capsule of zolpidem. (Berthelon et al., 2003) In a real world, however, zolpidem is frequently consumed not only by sleep disorder patients without any other comorbidities, but also patients with multiple chronic diseases. A post-marketing study of zolpidem revealed the incidence of the residual daytime sedation being 3.7%, (Ganzoni et al., 1995) which was reported to be unlikely based on various experimental circumstances with selected participants demonstrating negligible impairments. (Vermeeren, 2004) In fact, several studies with real world settings have reported positive relationship between the zolpidem and the traffic accident. (Gibson et al., 2009; Gustavsen et al., 2008; Orriols et al., 2011) while evidence among Asian population is scant.

Recent analysis of national health insurance data of Taiwan showed use of zolpidem at night of the previous day might be associated with an increased risk of MVC related hospitalization. (Yang et al., 2011) The study used 1 million patient sample data of whole Taiwan population to identified hospitalized drivers with MVCs and prescription record of the zolpidem before the hospitalization. However, the inclusion of MVC leading to only hospitalization might have led to underrepresentation of fatal cases that had no admission record. Moreover, the study was limited by lack of control for important confounders, because no information on detailed context of MVCs or alcohol consumptions was available. We aimed to evaluate the risk of fatal MVCs by use of zolpidem considering the context of the MVCs.

METHOD
Data source
To overcome the limitations of Taiwan study, we used data of fatal MVCs from Traffic Accident Analysis System (TAAS) maintained by the Korean Road Traffic Authority between 2010 and 2014 linked to the 2009–2014 National Health Insurance Data (NHID) from the Korean National Health Insurance Service (NHIS), using each individual's national identification number as a matching key. (Jung et al., 2016) The TAAS data contain details on the MVC including calendar date, time, location, weather, road condition, speed limit of the site, drinking status by blood alcohol levels etc. A fatal MVC was defined as an accident where the driver died within 30 days after the MVC. NHID contains all prescription and diagnosis information from a mandatory national insurance program of Korea whose details were available from other publication. (Cheol Seong et al., 2016) The present study has been exempted from review by the Institutional Review Board of Seoul National University Hospital (IRB number: E-1507-089-689).

Participant
Inclusion criteria were drivers who died of MVCs in 2010-2014 and received prescription with any zolpidem before the fatal MVCs. We excluded those with blood alcohol level was higher or equal to 0.05%.

Study design
To measure the transient effect of zolpidem on the incidence on the fatal MVCs, we adopted the case-crossover design where the patient themselves at different time periods served their own controls. (Maclure, 1991) The design had advantage in controlling the time invariant confounders which could not be measured in detail i.e. life style factors, driving habits etc. We matched 4 control periods to each
case period of the patients, with length of the exposure window is 1 day and interval of the case and control periods 90 days.

**Assessment of medication exposure**

Using NHIS formulary, we identified codes for the zolpidem and other medications that could be related to MVCs. The list of confounding medications was made based on ATC classification including sedatives/hypnotics except for zolpidem, anticonvulsants, antidepressants, antipsychotics, antiemetics, muscle relaxants, antihistamines and narcotics.

**Statistical analysis**

Patient characteristics and accident characteristics was presented with descriptive statistics. Age was categorized into <65, or ≥65. Charlson comorbidity index (Quan et al., 2005) was calculated and categorized into <5, or ≥5. The accident characteristics in TAAS data were summarized into the responsibility score (RS), which was developed to assess culpability of drivers. (Robertson et al., 1994) RS was further stratified into culpable range (RS<12), non-culpable or contributable range (RS≥12). Conditional logistic regression was performed to calculate the (OR) for fatal MVC by the exposure of zolpidem in the hazard periods compared to the control periods. The OR was adjusted for time varying exposure of confounding medications. Stratified ORs and 95% CIs were calculated for age (<65 or ≥65 years), comorbidity index score (CCI) score (<5 or ≥5), culpability (RS<12 or RS≥12), and prescription records of zolpidem 1 year prior to the study period to assess associations in new users. All statistical tests were 2-sided, and the statistical analysis was performed with SAS software (version 9.4; SAS, Institute, Inc., Cary, NC, USA).

**RESULTS**

During 2010-2014, 8,880 drivers died within 30 days after MVCs, we succeeded in linking the police report of 8,828 patients to the national health insurance claims data. After exclusion of drivers under the influence of alcohol, 7,061 patients remained, of whom 714 had prescriptions of zolpidem. Male patients were 650 (91.4%), mean age was 61.6 (standard deviation 14.3). Patients with age ≥65 were 349 (48.9%), CCI score ≥5 were 356 (49.9%). Sleep disorder diagnosis was found in most of patients 668 (93.6%).

Majority of accidents occurred during daytime 525 (73.5%), on dry roads 603 (84.5%), under the clear sky 589 (82.5%). Single vehicle accident was 355 (49.7%). RS with culpable range (<12) were 188 (26.3%).

The frequency of the having prescribed zolpidem in the hazard period and the control periods was 105 (14.7%) and 354 (12.4%), respectively. In the conditional logistic regression analysis, the OR was 1.48 and 95% CI was 1.06-2.07, which suggested statistically significant increase of the risk of fatal MVCs by zolpidem. After stratification, significantly increased risk was observed in the group with high CCI score (CCI≥5: adjusted OR: 1.81; 1.16-2.84), the younger age group (age <65; adjusted OR: 1.62; 1.03-2.56). When stratified with RS, both group showed similar adjusted ORs, however, the aOR were not statistically significant. (nonculpable or contributable drivers: 1.46; 0.98-2.18, culpable drivers: 1.56; 0.84-2.91) While patients with a record of prescriptions for zolpidem 1 year prior to the study period showed a diminished risk estimate, without statistical significance (adjusted OR: 1.22, 95% CI: 0.83-1.79), new users of zolpidem during the study period demonstrated a borderline significant increased risk of a fatal MVC (adjusted OR: 1.56; 95% CI: 0.98-2.50, p=0.0621).
DISCUSSION

Our finding added evidence that zolpidem prescription at the previous day was related to an increase in the risk of fatal MVCs. The ORs in our study were not bias by alcohol consumption since we have excluded drivers under influence of alcohol, and the driving habit and alcohol consumptions were assumed to be constant during the study period. Similar ORs in the high RS and the low RS group could be interpreted as the effect of zolpidem not being different between the groups, where the drug did not have any interaction with outer environment or condition of vehicle.

Our findings provide evidence that the risk of a fatal MVC associated with zolpidem is as high as that of traffic accidents resulting in hospitalization among an Asian population. (Yang et al., 2011) The possible underlying mechanism for this relationship has been explained in several ways. First, the residual effects of zolpidem could affect driving ability. Secondly, movement-based parasomnias, which include sleep-driving, have been reported as adverse events of zolpidem. Lastly, fatal MVCs in zolpidem users might be partially considered to be the consequence of perilous driving as a form of suicide attempt. A borderline significant risk of fatal MVCs was shown in new zolpidem users. This could be explained by considering that results among prevalent drug users in observational studies do not properly reflect patients who experienced early adverse drug events, and prevalent users have a tendency of better adherence to the drug than new users. In this study, a higher OR in patients younger than 65 years old was found, whereas the association was not significant in the elderly. The absence of an association in older drivers may be explained by their driving patterns, which have been reported to include a lower travel speed, increased seatbelt use, and increased self-regulation of driving. In conclusion, our study demonstrates that zolpidem use on the previous day was associated with an increased risk of fatal MVCs in an Asian population. Considering the increasing use of zolpidem, more caution is needed for both drivers and healthcare professionals.

REFERENCES


Quan, H., et al. (2005). Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care, 43(11), 1130-1139.

