Executive Summary

Objective

There were concerns regarding the potential over-prescription of Benzodiazepines (BZD) due to their nature for dependency and addition. Prescription patterns and safety related issues for BZD were studied in several countries. But, there were few recent prescription pattern studies and the safety related with BZD use were rarely studied in Korea. Since January, 2010, the limitation of ≤30-day supply for sedative hypnotics including BZD was implemented in Korea due to the possibilities of their inappropriate use. Assessment whether this policy that decreased the use of BZD would be required in terms of public health aspects.

The objective of this study is as follows.

-To review literatures on inappropriate medication use, safety, and social-economic costs related with BZD use
-To investigate prescription patterns of BZD in South Korea between 2007 and 2011
-To investigate the association between fracture and BZD presciption in South Korea

Literature review

□ Methods

Using the database of Embase and Ovid-Medline, literatures on inappropriate medication use, safety, and social-economic costs related with BZD use were searched. The search strategy comprised controlled vocabulary such as MeSH (Medical Subject Headings) terms

and keywords. Methodological filters were applied to restrict the study types such as health technology assessments, systematic reviews, meta-analysis, economic studies, guideline, and randomized controlled studies. From Jan, 2005 to March, 2012, 798 literatures from Ovid-Medline and 3569 literatures from Embase were selected. After removal of duplicated literatures, 3879 literatures were selected. Firstly, 591 literatures were selected through the title review, and then 382 literatures were selected through the review of abstract. In reviewing of full texts, prescription/treatment pattern (n=10), clinical practice guidance (n=20), motor vehicle accidents (n=6), suicide (n=7), cognitive impairments (n=12), fall and fracture (n=7), pregnancy (n=3), and interventions related with BZD appropriate use (n=7) were finally selected.

□ **Results**

The percentage of people who filled BZD prescription of at least once was 8.4-18.6% during one year in all population without restriction of age. It was 3.9-14.5% and 3.3 -9.5% among adult population of >= 15 years old and of 15-64 years old, respectively. Among the elderly of 65 years old or more, it was 16.0-31.7%. The percentage of people who filled BZD prescription was lower using survey methods than claim database.

All the clinical practice guideline recommended that BZD were not recommended as the first line treatment for the mood and behavioral disorder, panic disorder, and insomnia. In particular, they recommended that health professionals should be cautiously prescribed BZD for the elderly. The use of long acting BZD and long term use were not recommended for the elderly. For the treatment dementia, the use of BZD may produce the benefits to reduce the psychotic symptoms and agitation/aggression that outweigh the risk of adverse events such as fall and confusion. The use of short-acting

BZD and the dose adjustment were recommended for dementia patients.

The use of BZD increased the risk of fall/fracture and motor vehicle accidents. When BZD used concomitantly with opioid, the risk of suicide commitment increased. In few article said that the evidence for the association between delirium and BZD use were not sufficient. But, most of article reported the higher possibility of adverse events of delirium related with BZD.

In western countries, numerous strategies (i.e. exclusion of BZD from reimbursement list or limitation of 30-day supply) related with the restriction of BZD prescription were implemented. But, these policies led to a moderate decrease of BZD prescription, but it was likely to increase alternative medicines such as serotonin-specific reuptake inhibitor (SSRI) or tricycle antidepressants and affected more for vulnerable people who were lower socio economic status and chronic mental health disease. In addition, several articles reported that educational program for general practitioners or patients improved appropriate use of BZD.

Prescription Trends of BZD using Health Insurance Review and Assessment (HIRA) Database

□ **Methods**

We selected study subjects by 5% random sampling from adult patients (≥18 years old) who visited clinics or hospitals and have prescription of BZD from Jan.1, 2007 to Dec.31, 2011 using HIRA database. BZD was defined using WHO ATC Index, HIRA drug master file, and etc and was grouped by short-acting, long-acting, and BZD like drug (Z-drug). Defined Daily Dose(DDD) by WHO was used to

analyze the data in terms of dose and periods of BZD prescription. Data analysis was performed by claim unit or patient unit. For the analysis of patient unit, each claim was merged by same patient. In patient unit analysis, weight value of 20 was multiplied in order to convert 5% sampling data into national data. Prescription patterns of BZD were presented by subgroup of inpatient vs out-patients, long-acting vs. short-acting vs. Z-drug, and indication for BZD prescription.

□ **Results**

Data analysis by claim-unit base

Among total BZD claim of 1,989,263, the percentage of BZD claims for inpatient and out-patients was 94.6% and 5.4%, respectively. One claim included average 1.56 active ingredients of BZD. The percentage of claim for short-acting, long acting, and Z-drug was 52.6%, 40.6%, and 6.7%, respectively. When BZD claims were classified by sex, the percentage of claim for women and men was 65.1% and 34.9%. Clinics were most frequent provider for BZD prescription (77.1%) when medical centers were divided by clinics, hospitals, and general hospital. Most frequent prescribing active ingredient was diazepam, and gastro-duodenal diseases was the most frequent indication for BZD prescription. (29.8% among out-patient claims and 14.7% among in-patient claims)

Data analysis by patient-unit base

BZD prescription of at least once during five years occurred for a total of 22,361,449 patients (≥ 18years old) using 5% sampling data. The average national prescription prevalence per 100 people per one year was 23.7%, 7.9%, 4.7%, and 3.2 % for BZD annual prescription of ≥1day, ≥30days, ≥ 90days, and ≥ 180days, respectively using total number of population (≥18 years old) during study periods. Among elderly people of ≥ 65 years old, 46.0%,

23.3%, 15.2%, and 10.7%, respectively. Subgroup analysis was similar to claim data analysis. Clinics were most frequent provider of BZD prescription and the prescription prevalence was higher in the elderly (≥65 years old) than younger people (<65 years old), women than men, non-psychiatric department than other departments, and non-mental disease than mental disease. The frequency of prescription of short acting and long acting were similar, and Z-drug was prescribed to subjects of <10%. Among the elderly in an out-patient setting, long-acting was slightly higher than short acting BZD. In terms of one day dosage, overall BZD dosage was lower than average one day dose defined by WHO. DDD per 1000 population per one day was 109.2. Among the subjects who were prescribed to BZD, the subjects with the prescription of 1 DDD or more were about 10%. The average prescription days per one year were 129days for the elderly and 62days for younger subjects (18-64 years old) Among 100 population (≥18 years old), 1.79 subjects had BZD prescription of continuous 30-day supply or more. Among the elderly who were prescribed to long-acting BZD, those who have COPD diagnosis were 10.6% for men and 5.5% for women. The subjects with new BZD prescription (defined as the subjects who had no BZD presciption over previous one year) were about 56.6% among people with BZD prescription. The subjects who had BZD prescription over 90-day supply and 180-day supply were 5.62% and 2.46% among subjects with new BZD prescription, respectively.

Outcome study using Health Insurance Review and Assessment (HIRA) Database

□ **Methods**

This study used case-crossover design and self-controlled case-series design to investigate the association between fracture and

prescription of BZD. These study designs used case only and had merit to control confounding bias such as individual medical and demographic characteristics. Patients with fracture was defined that patients visited emergency room and orthopedics with ICD-10 diagnosis code of fracture. If they had fracture due to the motor vehicle accident and stroke, they were excluded. Whereas case-crossover design presented Odds Ratio(OR) and 95% Confidence Interval (CI) using conditional logistic regression model, self-controlled case-series design showed incidence rate ratio(IRR) and 95% CI using conditional poisson regression model. Subgroup analysis by short-acting vs. long-acting vs. Z-drug and the kind of active ingredient were conducted. The OR and IRR value including 95% CI were presented by sex and age group.

□ **Results**

Case-crossover design

A total of 3,325 patients with fracture was selected among 461,584 people who were prescribed to BZD in 2009. ORs for fracture among people who were prescribed to BZD were about 1.5 times higher than people who were not prescribed to BZD. Using control period of before 150-151 days from case periods, OR was 1.48 (95% C.I.: 1.16, 1.90). Sensitivity analysis using different control periods (before 90-91 days and before 120-121 days from case development) showed similar results. The elderly who were prescribed to long-acting BZD showed higher OR than other groups. Patients with short-term prescription had higher ORs than people with long-term prescription. (OR=1.24, 95% C.I.=0.92-1.66 for long-term vs. OR=2.32, 95% C.I.=1.46-3.70 for short term).

Self-controlled case-series design

A total of 6,623 patients with fracture was selected from 264,290 people who were newly prescribed to BZD in 2009. When patients

who had BZD prescription during one month of Jan, they were excluded to put non-exposure period of one month. IRR for fracture among people who were prescribed to BZD were 1.87 times (95%CI=1.72-2.03) higher during initial four week periods than non exposure periods. IRR was lower when exposure periods were longer. Subgroup analysis was in accordance with the main results.

Conclusion

Overall BZD dosage was lower than WHO defined daily dose, but BZD prescription was frequent. The average national prescribing prevalence per 100 people per one year was 23.7% for ≥1day, 7.8% for ≥30days, 3.2% for ≥ 180days, respectively using total number of population (≥18 years old) during study periods. BZD prescription was much frequent among elderly people of ≥ 65 years old and one-year prescription trend was similar during five years of study periods. BZD prescription much occurred at out-patient visit in clinics than other types of medical centers. When they were classified into kind of active ingredient, the prescription of diazepam , one kind of long-acting BZD, was most frequent. BZD was prescribed more for the indication of gastro-duodenal disease than neuro-psychological diseases. The risk for fracture was higher in patients with BZD prescription than people without BZD prescription. In particular, elderly people who were 65 years old and were prescribed to long-acting BZD had higher OR than other groups. The people with short-term BZD prescription or exposure in early period from BZD initial prescription had trends of higher risk for fracture than those with long-term or exposure in late period.

From the lesson on the experience of western countries, policy implementations such as limitation of supply periods and exclusion

from reimbursement list were likely to increase alternative medicines and affected more for vulnerable people who were lower socio economic status and chronic mental health disease. The validity for educational program for general practitioners or patients which was reported as effective measures in other countries would be investigated for appropriate use of BZD.