NECA National Evidence-based Healthcare Collaborating Agency
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National Evidence-based Healthcare Collaborating Agency

THE EVIDENCE

Prescription pattern and safety of benzodiazepines

Introduction

Brom, chloral paraldehyde, and barbiturates, which were used as sedatives or hypnotics before the 20th century, showed high effectiveness, yet caused dependency and serious withdrawal symptoms after long-term use. Later, in the 1960s, benzodiazepines (BZDs) were developed. As they have a similar efficacy yet cause adverse effects than the drugs of prior generations, they have been used as a cure for anxiety disorders and insomnia up to the present. However, many countries have recently pointed out problems with overuse of and dependency on BZDs.

In addition, abrupt discontinuation of the drugs after long-term use has been reported to provoke withdrawal symptoms including perspiration, vomiting, irritability, convulsions, abdominal pain, myalgia, hallucinations, and epilepsy (Lader, 2011). In particular, it is recommended that BZDs be administered with caution to elderly patients (Fick, 2003). Long-acting agents such as diazepam and flurazepam, which are BZDs, have a longer half-life in the elderly and thus the risk of excessive sedation, falls, and fractures is increased if administered for a long period of time. While the patterns of drug use and side effects are being widely studied internationally, research in Korea has mainly focused on identifying the elderly's pattern of use of the drugs (Yang, 2001; Kong, 2005; Kim, 2008).

Recently, the importance of mental health has been gaining public attention. At the same time, in the wake of the implementation of institutions such as the establishment of a medication prescription/preparation support service (Drug Utilization Review, DUR), limiting the number of days of prescriptions (January, 2010)[1], and restrictions in administration of psychotropic medications (May, 2011)[2], which was aimed at promoting the appropriate use of BZDs—the most representative drug—a preemptive study to identify the current status of drug use and the degree of side effects in Koreans is necessary.

1) For sedative/hypnotics prescribed for injuries or diseases such as insomnia and sleep disorders for the long term without a doctor's supervision, the number of days of prescription is approved to be no more than 30 days per prescription. However, for triazolam, the number of days of prescription is approved to be no more than three weeks per prescription with reference to the Korea Food and Drug Administration (KFDA).
2) In principle, for psychotropic medications, one item can be administered within the range of approval by the head of the KFDA.

This issue paper is written based on the research results performed by the National Evidence-based Healthcare Collaborating Agency (NECA).
The full texts of the research report is available from the website of NECA (www.neca.re.kr).

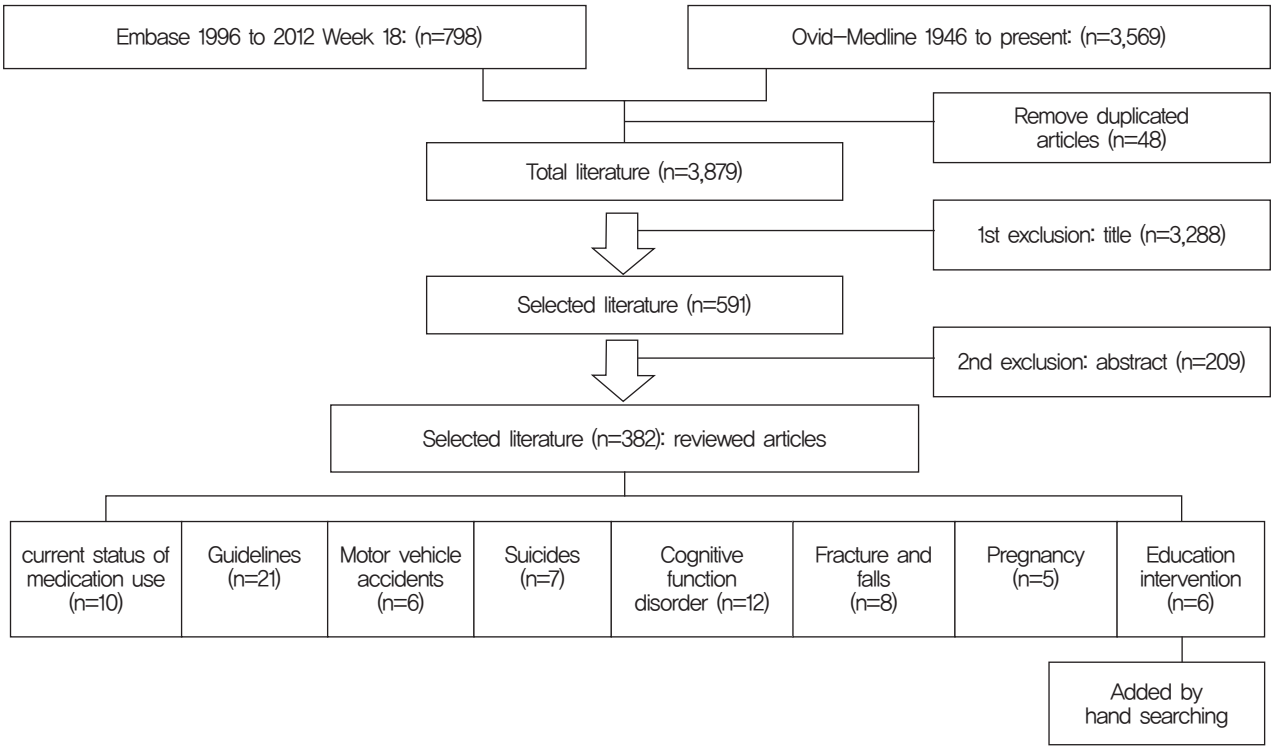

Figure 1. Flow-chart of literature selection process

Literature review on BZDs

Research method

Through literature searches of the databases Embase and Ovid-Medline, we selected literature on the use of BZDs that used the following as outcome variables: ① the level of inappropriate use and misuse; ② safety issues and socio-economic loss.

For literature on guidelines and interventions related to education, we added studies through a hand search of the literature selected from Embase and Ovid-Medline. After short-listing the literature, we reviewed the original articles and classified them according to topic: the current status of BZD use (10 articles); guidelines (21 articles); motor vehicle accidents (6 articles); suicides (7 articles); cognitive function disorders (12 articles); fractures and falls (8 articles); pregnancy (5 articles); and education-related interventions (6 articles). Then we conducted a literature review.

Research results

A. Current status of prescription and use

In a study conducted on the residents of all age groups in a community, the rates of BZD use were 8.4-18.6%. According to a study conducted on adults over 15 years of age, 3.9-14.5% of the population had used the drugs at least once in the previous year. In another study conducted with people aged 15 to 64 years, the rates of use were 3.3-9.5%. In the elderly aged over 65 years, 16.0-31.7% reported having been prescribed or using BZDs at least once. Compared to the findings of research using insurance claim data to identify the current status, the findings of research using

surveys on population groups were likely to show less frequent use of BZDs.

B. Guidelines

The guidelines on the use of BZDs in and outside of Korea recommend that BZDs be used as a short-term adjuvant treatment method for mood disorders, behavior disorders, panic disorders, and sleep disorders. BZDs are not recommended for the elderly or individuals with psycho-behavioral disorders such as dementia to be used for a long term and as long-acting agents. They can be used for patients with clinical agitation, but dosage adjustment is necessary considering possible side effects, and short-acting agents are preferred.

C. Accidents and disabilities

The use of BZDs is known to have a significant association with the increased risk of motor vehicle accident occurrence, and the risk increased more when the use was combined with alcohol use. Also, among the population group, in the elderly, BZD use is associated with accidents such as falls, although its mechanism in relation to the length of time of use has not been clearly identified. In the meantime, the use of BZDs is reportedly relevant to cognitive function disorders, including delirium, and the risk is higher in the case of long-acting agent use. In particular, adolescents with untreated depression and individuals with depression with suicidal ideation experienced significantly more suicide-related side effects when using BZDs as an adjuvant therapy. In addition, BZDs used to treat depression and insomnia during pregnancy are known to increase the risks of cleft palate in newborns, delivery of infants of low birth weight, and preterm delivery.

D. Intervention programs

Institutions such as a prescription monitoring program to reduce the misuse of BZDs are found to lead to positive consequences, including a decrease in the amount of use and improvement in side effects. Nonetheless, the increase in the prescription of high-priced non-BZD drugs similar to BZDs and unevenness in the effect of the policies across various population groups in society have been identified as problems.

Besides institutional regulatory programs, direct and indirect education programs for doctors and patients were found to be effective in reducing the misuse of BZDs. Regular education for doctors and pharmacists about the risk of long-term usage of BZDs in the elderly and withdrawal symptoms resulted in a 26.6% reduction in prescriptions of the drugs.

Current prescription status based on HIRA claim data

Research method

Using claim data of the Health Insurance Review and Assessment Service (HIRA), we examined the prescription pattern of BZDs in Korea. The cases in which patients of age who were prescribed BZDs (as well as drugs similar to BZDs) from medical institutions once or more than once in the past five years (2007-2011) were reviewed. Among the total subjects in the analysis, we first screened subjects for analysis by 5% random sampling per year. Then we excluded patients prescribed with BZDs for conscious sedation endoscopy and patients whose ages were not identified per year and those younger than 18 years old, consecutively. Thus, in the end, we included 2,300,760 as the study subjects.

BZDs were selected based on the WHO ATC Index, HIRA

drug component code, and medical fee file, and the classification code of the Ministry of Health and Welfare, and the amount of drug use was analyzed using the Defined Daily Dose (DDD) of patients with the prescribed drugs[3]. For the final analysis, the claim unit and patient unit analysis were conducted. In the patient unit analysis, the weight value of 20 was multiplied in order to convert the 5% sampling data into the national population according to the prescription ratio.

previous five years: women (61.7-62.9%) outnumbered men (37.1-38.3%), and the number of patients who received the prescription ≥ 1 day, ≥ 30 days, ≥ 90 days, and ≥ 180 days per year were 23.7, 7.9, 4.7, and 3.2 per 100 persons (≥ 18 years old), respectively. In the elderly patients aged 65 or older, both men and women received more prescriptions than their younger counterparts. In the female elderly, the prescription rates for long-acting agents and short-acting agents were higher than in the male elderly (Table 1).

Table 1. Number of patients prescribed with BZDs per year: according to sex and age per 100 among the population ≥18 years old

Classification		Men		Women	
		< 65 years (n=17,143,249)	≥ 65 years (n=2,134,737)	< 65 years (n=16,495,240)	≥ 65 years (n=3,114,060)
Drugs	Total BZDs	15.3	39.8	25.0	52.0
	Short-acting	9.1	24.6	15.4	33.8
	Long-acting	8.1	23.8	14.0	32.8
	Z-drugs	1.4	6.9	2.6	8.5
Diseases	Neuropsychiatric	6.3	20.7	11.9	30.7
	Non-neuropsychiatric	9.2	29.4	16.6	43.0

Research results

The claim unit analysis results showed that, on average, 1.56 BZD components were included per claim, and the prescribed drugs were long-acting agents (52.6%), Short-acting agents (40.6%), and Z-drugs (6.7%) in order of frequency, and the most frequently prescribed component was diazepam.

According to the patient unit analysis, a total of 22,361,449 patients over 18 years old were prescribed BZDs in the

Regarding the clinical specialty, 88% of the patients who had been prescribed with BZDs once or more than once received the prescription from a non-neuropsychiatric department only, while 5% received the prescription from the psychiatric department only, including inpatient and outpatient services (Figure 2).

Regarding the type of medical institutions, 76% received a prescription from a local clinic; 14% from a tertiary hospital; and 10% from both clinics and tertiary hospitals (Figure 3).

3) This signifies the DDD of drugs used to treat the main indications in adults (WHO, 2009). The dose can change based on the characteristics of individual patients and pharmacokinetic characteristics.

※ Formula for calculating the amount of (BZD) use: [Total amount used per year × (Content of i, a component of BZDs÷Xi)/365]×1000/number of population(Xi:componenti's1DDD=Ximg(DDDIndex,WHO))

Table 2. Average prescribed daily dose of patients (≥ 18 years) prescribed with BDZs by year

Classification		DDD (mg)	Total inpatient & outpatient				Outpatient				Inpatient			
			Men		Women		Men		Women		Men		Women	
			< 65 years	≥ 65 years	< 65 years	≥ 65 years	〈65 years	≥ 65 years	< 65 years	≥ 65 years	< 65 years	≥ 65 years	< 65 years	≥ 65 years
Short-acting agents	Alprazolam	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.5	0.6	0.5
	Lorazepam	2.5	2.3	2.4	1.6	1.7	1.5	1.3	1.3	1.2	3.8	3.9	3.1	3.1
	Midazolam	15	8.2	15.2	6.6	9.7	5.2	5.4	5.3	5.5	11.0	21.0	7.5	11.6
Long-acting agents	Diazepam	10	7.3	7.0	7.1	7.0	7.2	6.9	7.1	6.9	8.0	7.7	7.7	7.1
	Clonazepam	8	0.7	0.7	0.7	0.6	0.7	0.6	0.6	0.6	1.0	0.7	0.9	0.7
Z-drug	Zolpidem	10-12.5	10.3	9.9	10.0	9.7	10.4	10.2	10.1	9.9	10.0	8.9	9.6	8.7

Outpatient patients were usually prescribed alprazolam as a short-acting agent, diazepam as a long-acting agent, and zolpidem as a Z-drug most frequently; inpatient patients were prescribed midazolam as a short-acting agent and the rest were the same as the outpatient patients. The result of the analysis on the average prescribed daily dose of BDZs included in the claims bill of the HIRA showed that most were using less or slightly more than the DDD of the drugs as defined by the WHO (Table 2).

Based on the total inpatient and outpatient treatment data, the average of total BDZs was 109.2 per 1,000 (≥ 18 years old) by year, and 2.39% patients were prescribed with over 1 DDD per 100 (≥ 18 years old) by year in Korea. By year, the total number of days of the prescription was 80 days on average: 62 days in < 65 years old; 129 days for ≥ 65 years old; 1.79 per 100 persons (≥ 18 years old) per year received a prescription for more than 30 consecutive days.

In addition, among patients prescribed with BDZs, in cases of patients who received the prescription for over 30 consecutive days, there were more patients diagnosed with neuropsychiatric diseases (9.8%) than those diagnosed with non-psychiatric diseases (5.9%).

In the last five years, 1,041,754 patients were newly prescribed with BDZs, and among them 5.62% were prescribed for ≥ 90 days and 2.46% for ≥180 days per year.

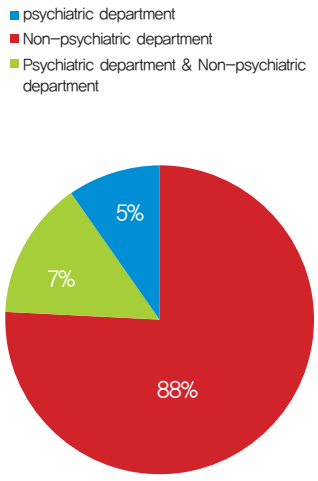

Figure 2. BDZ prescriptions by clinical specialty

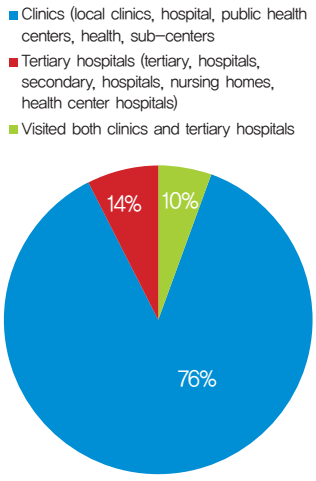

Figure 3. BDZ prescriptions by medical institution

Association between BDZs and occurrence of fracture

Research method

To analyze the effect of BDZ use on fracture occurrence, we applied a case-crossover design and self-controlled case-series design, using HIRA claims data (Table 3).

Research results

A. Case-Crossover Design

During the control period of 150 days, cases where BDZs were used had a 1.48 (95% C.I.: 1.16-1.90) higher adjusted odds ratio (OR) for fracture occurrence than cases where BDZs were not used. By gender, in the females, the odds of the occurrence of fracture were statistically higher (adjusted OR=1.64, 95% C.I.: 1.20-2.24).

The OR for fracture occurrence was higher in the patients with short-term prescriptions (adjusted OR=2.32, 95% C.I.: 1.46, 3.70) than in the patients with long-term prescriptions (adjusted OR=1.24, 95% C.I.: 0.92, 1.66). However, there was no major difference between the groups in the findings on the sensitivity analysis for each different window period (3, 7, and 14 days) and control period (90 days and 120 days).

B. Self-Controlled Case-Series Design

Regarding the fracture occurrence rate in each exposure period, the rate decreased as more time had passed since the first prescription of BDZs. The fracture incidence rate ratio (IRR) within 4 weeks since the first prescription of BDZs was 1.87 (95% C.I.: 1.72-2.03), and with a longer exposure period, the IRR tended to decrease.

Conclusion

This study has significance for analyzing the current status of BDZ prescriptions in Koreans (≥ 18 years old) using recent data from HIRA.

The prescribed dosages of BDZs were generally less than the DDD defined by the WHO. Yet, the prescription was being made too frequently. The prescription was particularly made more frequently for the elderly ≥ 65 years old. Between 2007 and 2011, the prescription pattern did not change.

The prescriptions of BDZs were provided frequently by outpatient clinics. By the type of drug, diazepam—a long-acting agent—was commonly prescribed, and it was prescribed for gastrointestinal diseases more than for neuropsychiatric diseases. Also, an association between fractures and prescription of BDZs was identified. Greater caution for adverse effects is needed in patients receiving short-term prescriptions than in patients newly taking the drugs or receiving long-term prescriptions.

In other countries, the introduction of regulatory programs to control the prescription of BDZs has been found to have weak policy effects on the increase of the prescription of similar and high-priced drugs, and on patients with chronic mental diseases or socially vulnerable ones with low-income. Therefore, for the appropriate use of BDZs, the introduction of proper education programs for medical professionals and patients is imperative, in addition to the restriction of duplicate prescriptions of psychotropic drugs and application of DUR (2011), which are currently being implemented.

Table 3. BDZ outcomes research design

Classification	Content
Definition of fracture patient	Patients who visited the ER or were admitted to the orthopedic surgery department due to fracture in 2009 (except for those who had a motor vehicle accident, had been diagnosed with stroke, or had a history of fracture [2007-2008])
Study design and analysis method	**<Case-Crossover Design (n=3,325)>** - (Inclusion) Fracture patients prescribed with BDZs in 2009 - (Exclusion) Patients prescribed with opioids within one year prior to the occurrence of the fracture - (Risk period) A day prior (D-1) to the first occurrence of fracture (D) in 2009 - (Control period) D-150 days (Window period D-151) * Conducted sensitivity analysis on the control period D-90 and D-120 * Additional window period 3, 7, and 14 days * Whether BDZs were prescribed was defined considering the number of days of prescription before the occurrence of fracture - The OR (95%CI) was obtained using a conditional logistic regression model * Adjusted for drugs that can affect fracture (confounder)
Study design and analysis method	<Self-Controlled Case-Series Design (n=6,623)> - (Inclusion) Fracture patients prescribed with BDZs for the first time in 2009 - (Exclusion) Individuals prescribed with BDZs for one month in January 2009 Individuals who had no fracture occurrence in 2009 - (Non- exposure period) 4 weeks before the first prescription of BDZs - (Exposure period) 4 weeks, 4-8 weeks, 8-12 weeks, and 12-16 weeks after the first prescription of BDZs * The continuously prescribed ones are defined as those who claimed another prescription within 7 days of the end of the previous prescription - IRR (95%CI) is calculated using conditional Poisson regression model

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Research Team

Principal Investigator

Jin-Won Kwon College of Pharmacy, Kyungpook National University

Participating researchers

Jin Seb Hwang NECA
Sung-Hee Oh NECA
EunJeong Park NECA
Su Jin Kwak NECA
Kang Seob Oh Department of Psychiatry, School of Medicine, Sungkyunkwan University
Kyoung-Uk Lee Department of Psychiatry, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, College of Medicine
Boung-Chul Lee Department of Psychiatry, Hangang Sacred Heart Hospital, Hallym University
Jong-Min Woo Department of Psychiatry, Inje University Seoul Paik Hospital

NECA National Evidence-based Healthcare Collaborating Agency

Publication and Inquiry: Research Appraisal Department of NECA
E-mail: jhr230@neca.re.kr