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ORIGINAL PAPER

Concurrent use of benzodiazepines, antidepressants, and opioid analgesics with zolpidem and risk for suicide: a case–control and case–crossover study

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Abstract

Purpose To evaluate whether the concurrent use of benzodiazepines, antidepressants, and opioid analgesics with zolpidem increases the risk of suicide or triggers suicide compared with the use of zolpidem alone.

Methods We conducted a case–control and case–crossover study using the Korean National Health Insurance Service-National Sample Cohort database. Cases were older than 20 years with a suicide record (International Codes of Disease 10th Revision codes: X-60-X84 and Y87.0 intentional self-harm) between January 1, 2004, and December 31, 2013. For case–control design, ten controls were matched to each case by age, sex, index year, region, income, and health insurance type. For case–crossover analysis, we set hazard period to 60 days and assigned five corresponding sets of control periods of equal length. Exposure was assessed during 60 days before suicide for combinations of benzodiazepines, antidepressants, opioid analgesics with zolpidem against zolpidem alone. We conducted a conditional logistic regression to estimate odds ratios (ORs) and their 95% confidence intervals (CIs).

Results In the case–control study, the risk of suicide was 2.80-fold higher in cases taking benzodiazepines and antidepressants with zolpidem than in those taking zolpidem alone (adjusted OR [aOR], 2.80; 95% CI, 1.38–5.70). However, in the case–crossover study, suicide risk showed no significant difference (crude OR [cOR], 0.92; 95% CI, 0.55–1.52) and was underpowered.

Conclusions The results of the traditional case–control study confirmed that the concurrent use of benzodiazepines and antidepressants with zolpidem was associated with an increased risk of suicide compared with the use of zolpidem alone. However, there was no significant difference in the magnitude of risk in the within-person comparison design.

Keywords Zolpidem · Concurrent · Benzodiazepine · Antidepressant · Opioid analgesic · Suicide

Introduction

Zolpidem is a rapid-onset, short-acting non-benzodiazepine hypnotic used for the treatment of insomnia [1, 2]. It is believed to be a safer alternative to benzodiazepines for the treatment of insomnia, having lower risks of both toxicity and dependence [3, 4]. However, concerns have been reported in the past decade as prescriptions of zolpidem have increased [5–9]. One of the most fatal concerns is regarding suicide, as the FDA's post-marketing safety review of the zolpidem in 2006 included additional adverse event reports. The FDA report summarized several suicide cases that occurred within a week of the initial dose of zolpidem [10].

Benzodiazepines [11, 12], antidepressants [13], and opioid analgesics [14] are also suspected to increase the risk of suicide. Three cross-sectional studies [9, 15, 16] and one cohort study [17] showed that unsafe combination of these drugs is common when trying to improve insomnia in depression or chronic pain patients [18–23]. A case-series study between 2001 and 2010 in Australia reported that zolpidem alone as well as the combined use of zolpidem

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with other drugs, such as benzodiazepines, antidepressants, opioids, and alcohol have been implicated as causal agents in many suicide cases [24]. A study in Norway between 2000 and 2009 reported that benzodiazepine, analgesic, and antidepressant use was more frequently detected in suicides than in accidental deaths or homicides [25].

In previous studies of suicidal individuals, altered γ-aminobutyric acid (GABA) or serotonin levels have been observed [26–33]. Zolpidem is a derivative of imidazo-pyridine, which has a different molecular structure than those of benzodiazepines. However, the pharmacological actions of zolpidem are similar to those of benzodiazepines because these drugs involve the benzodiazepine receptor site, which is associated with GABAa receptors. Central nervous system (CNS) depressants, such as benzodiazepines, opioid analgesics, and antidepressants act on neurotransmitters, including GABA and serotonin also. Thus, increased risk of suicide in zolpidem users from previous studies (risk ranging from 1.94 to 3.4) [11, 34–36] may be the result of concurrent use of zolpidem with benzodiazepines, antidepressants, and opioid analgesics. However, no epidemiological study has quantified the increased risk of suicide in patients taking multiple medications with respect to the use of only zolpidem. In addition, presence of comorbid psychiatric disorders may be a crucial confounding factor associated with the risk of suicide; however, such between-person characteristics had not been thoroughly considered.

Therefore, our study objective is to evaluate whether the concurrent use of benzodiazepines, antidepressants, and opioid analgesics along with zolpidem increases risk of suicide when compared to use of zolpidem alone, by the application of case–control and case–crossover designs.

Methods

Data source

The Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) database ($n = 1{,}113{,}656$; January 1, 2002–December 31, 2013) was used for this study. The South Korean NHIS system includes the entire national population (~50 million people), and the database was established for claim reimbursements. The NHIS collects healthcare utilization records through claim data, which includes information on inpatient and outpatient records. Medical usage (diagnosis, length of stay, treatment costs, and services received) and prescription (drug code, prescription initiation date, total prescription days, and daily dosage) records are created by medical institutions for cost reimbursement by NHIS. The Korean NHIS-NSC database was constructed by the NHIS for health-related research. For sampling, 756 strata based on variables such as 18 groups for age, 21 groups for income level by insurance type (ten groups for NHIS district subscribers, ten groups for NHIS employee subscriber, one group for medical aid), and sex were set up using 2002 data. The sampled individuals were followed until 2013. Data regarding subject characteristics, clinical information, socioeconomic level, and death information were included in the database. Clinical information including disease diagnosis codes based on the International Codes of Disease 10th Revision (ICD-10), clinical modifications, treatments based on drug prescriptions and health care costs were recorded. Death information, including cause of death code from the South Korea Vital Statistics database, based on the International Codes of Disease 10th Revision (ICD-10), was also recorded in the Korean NHIS-NSC database. A previous validation study compared causes of death from the South Korea Vital Statistics database to those from hospital medical records. The study reported a 92% agreement [37].

Case and control selection

We, at first, conducted a population-based case–control study. Case of suicide was defined as the patient with a record of suicide (ICD-10 codes: X-60-X84 and Y87.0 intentional self-harm) in the Korean NHIS-NSC database. The index date was defined as the date of the suicide record as either a suicide death or suicide attempt. The patient with a record of suicide before December 31, 2003, at an age younger than 19 years, or whose date of first zolpidem exposure was on or later than the index date was excluded from the case selection. A flowchart of the inclusion and exclusion criteria is shown in Fig. 1.

Suicidal behavior shows marked differences between sex, age groups, geographic regions, and socio-political realities. Thus, for the case–control study, we randomly matched ten controls without a record of suicide event to each case at the year of index date according to age group (per 5 years), sex, region, income level (categorized into four levels), and type of health insurance.

Exposure definition

We obtained patient's medication histories for benzodiazepines (ATC codes: N03AE, N05BA, and N05CD), antidepressants (N06AA, N06AB, N06AG, and N06AX), opioid analgesics (N02AA, N02AB, N02AD, N02AE, N02AF, N02AX, and N01AH), and zolpidem (N05CF02) during a period of 2 years before the index date and tracked medication use trends over time. The study medications in addition to zolpidem are shown in Supplementary Table 1.

Using the prescription information (prescription initiation date and total prescription days), we measured the drug prescription periods and defined concurrent use as

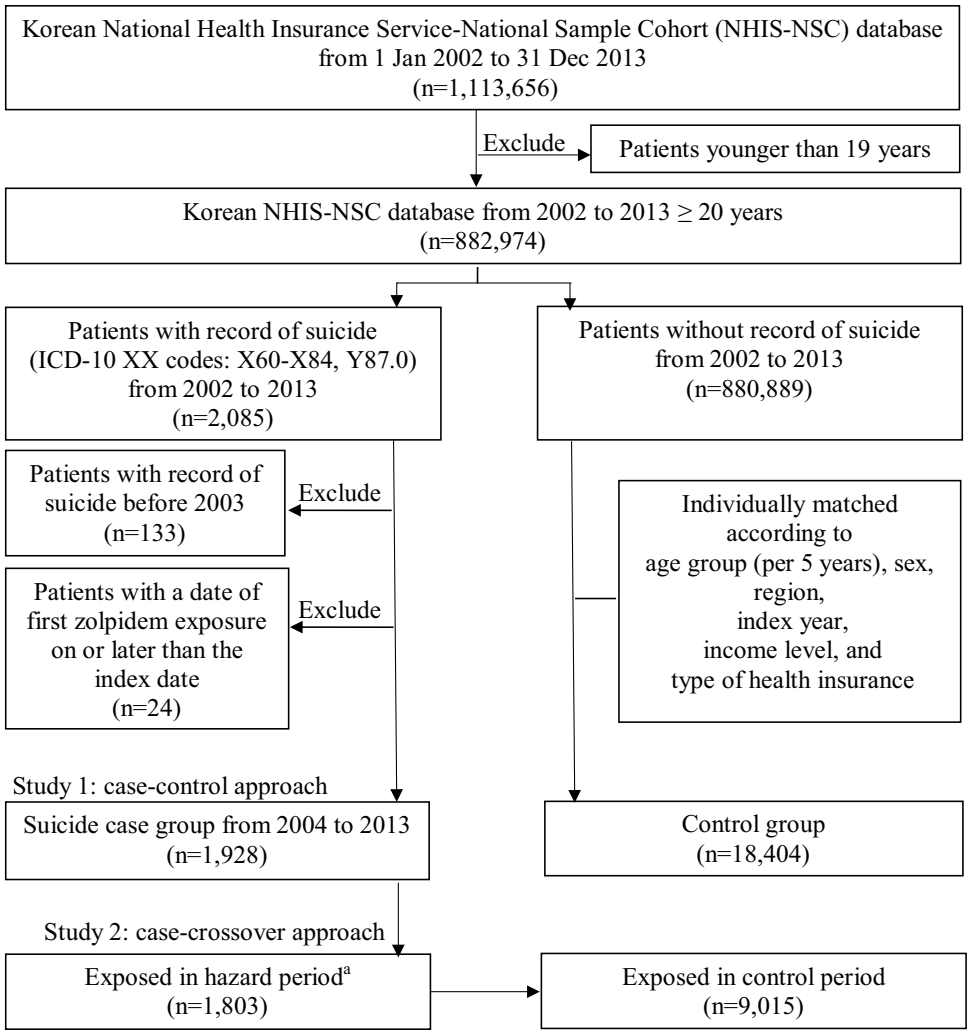

Fig. 1 Flowchart for selection of study population for case–control and case–crossover studies; ICD-10: international classification of disease, tenth revision. [a]Each enrolled case for the case–crossover approach has been restricted to subjects who had used the drug at least once in the hazard period or control periods

when the prescription period of a drug overlapped with that of another drug during the time window before the index date. One or more days of overlap qualified as concurrent use.

At first, exposure was categorized into 15 mutually exclusive groups according to the combination of benzodiazepines, antidepressants, opioid analgesics, and zolpidem. It was assessed for the period of 60 days before the index date. Only the results of the eight mutually exclusive groups, including the zolpidem, were displayed for comparison: (1) zolpidem only use (reference group): (2) concurrent use of benzodiazepines and zolpidem: (3) concurrent use of antidepressants and zolpidem: (4) concurrent use of opioid analgesics and zolpidem: (5) the concurrent use of benzodiazepines, antidepressants, and zolpidem: (6) concurrent use of benzodiazepines, opioid analgesics, and zolpidem: (7) concurrent use of antidepressants, opioid analgesics, and zolpidem: (8) concurrent use of benzodiazepines, antidepressants, opioid analgesics, and zolpidem.

Case–crossover design

We also conducted a case–crossover study, a design that was introduced in 1991 by Maclure [38]. The case–crossover design is a within-subject technique that uses each case as its own control, instead of comparing it with other individuals. In the case–crossover design, time-invariant characteristics among individuals (e.g., age, sex, chronic substance use, and childhood abuse) are eliminated by design. This design is ideally suited to assess acute trigger effects in association with intermittent short-term exposure, as opposed to chronic effects [38]. Case–crossover designs investigating the association between substance use and suicidal behavior have previously been studied [39–41].

Each enrolled case for the case–crossover analysis has been restricted to subjects who had received the drug at least once during the hazard period or control periods. A flowchart of the inclusion and exclusion criteria is shown in Fig. 1. We defined the hazard period to be 60 days before the

index date. A single hazard period matched with five prior sets of 60-day control periods with 14-day washout periods between hazard and control periods. The study scheme of case–crossover study of zolpidem and suicide is shown in Fig. 2. Discordant pairs for exposure between hazard and control periods were only used to estimate the odds ratio (OR) in the case–crossover analyses.

Potential time-varying confounders

Comorbid mental disorders (ICD-10: F00-F99) were considered to be the main confounding factors and were assessed during 1 year before the index date: schizophrenia spectrum disorders (F20, F21, and F25), major depressive disorder (F32 and F33), other type of depression (F34.1 and F43.21), bipolar disorder (F31), anxiety (F41), substance use (F10-19), insomnia (G47 and F51), and other mental disorders (F99). Depression was classified as either "major depressive disorder" (ICD-10: F32 [depressive disorder] and F33 [recurrent depressive disorder]) or "other types of depression" (ICD-10: F34.1 [mood depression] and F43.21 [adaptive disorder]), which was relatively less severe. Patients who died by suicide or those who attempted suicide often have other comorbidities with mental disorders. Therefore, referring to previous patient diagnoses during a 1-year period before the index date, we calculated the Charlson comorbidity index (CCI), which is a weighted index of 19 chronic comorbid diseases (e.g., cancer, diabetes, myocardial infarction, moderate or severe renal disease, hemiplegia, liver disease, and chronic pulmonary disease) [42].

For the case–control study, the aforementioned mental disorders status and CCI between cases and controls were adjusted in the outcome model. In the case–crossover study, discordant pairs of these confounders between the hazard and control periods were adjusted in the model.

Statistical analysis

ORs and 95% confidence intervals (CIs) were determined by conditional logistic regression. We evaluated suicide risk for the concurrent use of benzodiazepines, antidepressants, opioid analgesics, and zolpidem with reference to that for zolpidem alone. The sensitivity analyses were performed by varying the time window of the exposure period from 60 to 30 days to evaluate the robustness of the results for both the case–control and case–crossover studies. For the case–crossover study, sensitivity analyses were performed by varying the number of controls from five sets of control periods (main analyses) to two or three sets of control periods to confirm whether the exposure trend affect the estimated OR. All statistical analyses were performed with SAS Version 9.4 (Statistical Analytical Software Institute). A *P* value of less than 0.05 was considered statistically significant.

Results

For the case–control study, we selected 1928 (1234 men, 694 women) cases and 18,404 matched controls. The demographic characteristics and comorbidities for the case and control groups is shown in Supplementary Table 2 from a study by Choi et al. [36]. The medication use trends of benzodiazepines, antidepressants, opioid analgesics, and zolpidem for the case–crossover study subjects during a period of 2 years before index date are shown in Fig. 3a. The medication use trends of the eight mutually exclusive combination groups for case–crossover study subjects are shown in Fig. 3b. In both figures, the trends of use for all study medications showed a bouncing pattern within 60 days before suicide. All study medications were elevated in the 60 days prior to the date of suicide.

Table 1 shows the adjusted OR (aOR) and corresponding 95% CIs of suicide risk associated with the exposure to the concurrent use of benzodiazepines, antidepressants, opioid analgesics, and zolpidem as analyzed using a traditional case–control study design. We observed that the concurrent use of benzodiazepines and antidepressants with zolpidem was associated with an increased risk of suicide compared with zolpidem alone (aOR, 2.80; 95% CI, 1.38–5.70). We observed that any other concurrent use of benzodiazepines, antidepressants, or opioid analgesics with zolpidem except for the aforementioned concurrent use showed no significant difference in suicidal risk than zolpidem alone. The results were quite consistent in the sensitivity analysis when

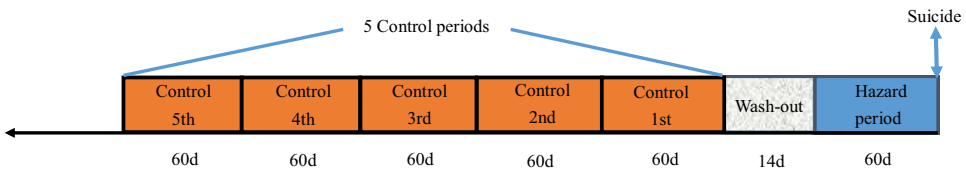

Fig. 2 Scheme of case–crossover study. The hazard period was defined as 60 days prior to the suicide adverse event. There was a single hazard period matched with five sets of control periods of 60 days, with the introduction of a 14-day washout period between the hazard and control period

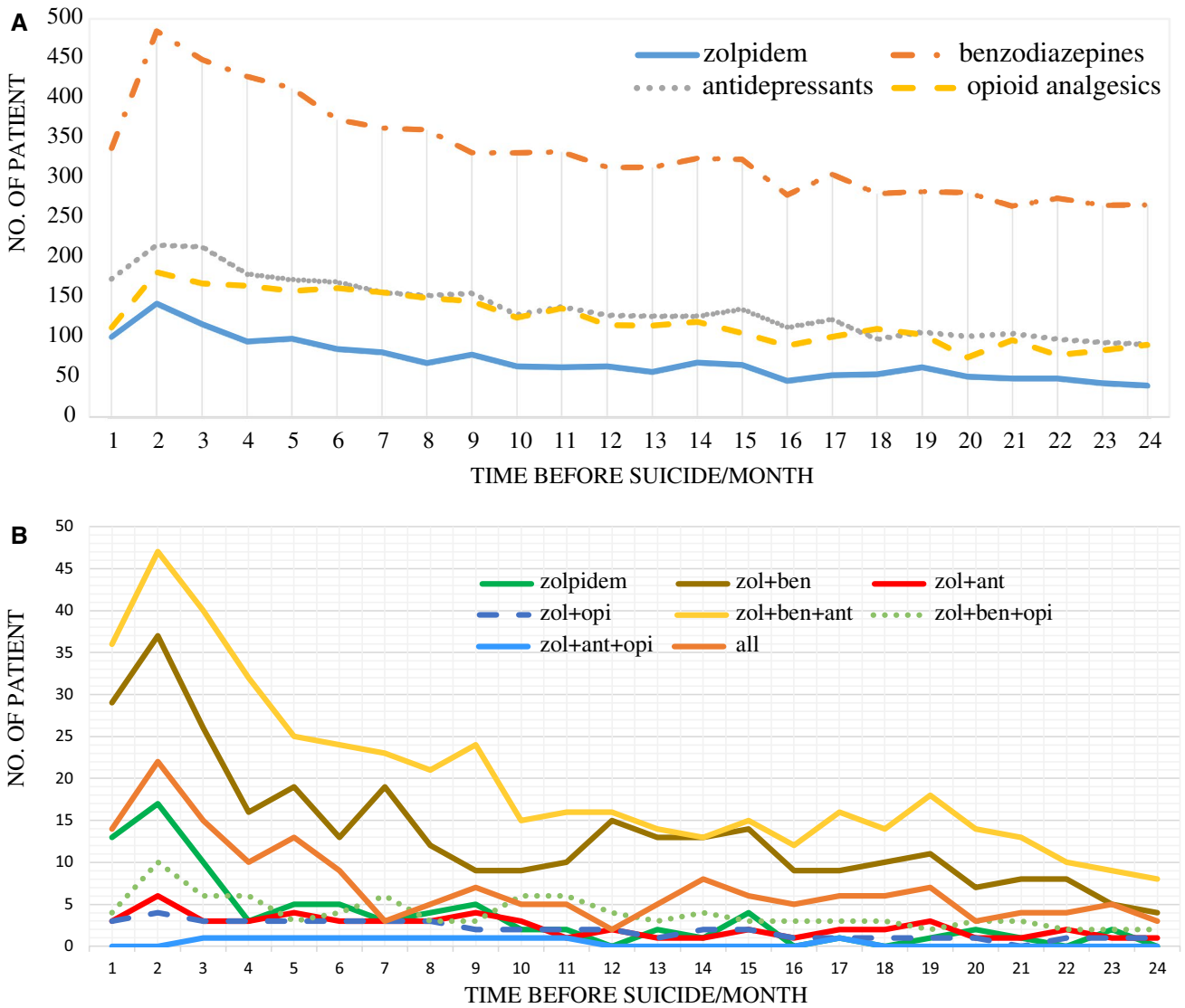

Fig. 3 **a** Medication use trends for case–crossover study subjects during a period of 2 years before suicide even. **b** Medication use trends of the eight mutually exclusive combination groups for case–crossover study subjects during a period of 2 years before suicide event. *zol* zolpidem, *ben* benzodiazepines, *ant* antidepressants, *opi* opioid analgesics

varying the risk periods from 60 to 30 days, except for the concurrent use of benzodiazepines and antidepressants with zolpidem, which was no longer significantly different for suicidal risk compared with zolpidem alone (aOR, 2.03; 95% CI, 0.97–4.25).

For the case–crossover analysis, we selected 1803 cases exposed during the hazard period and matched 9015 control periods. Table 2 shows the crude OR(cOR) and corresponding 95% CIs of suicide risk associated with the exposure to the concurrent use of benzodiazepines, antidepressants, and opioid analgesics with zolpidem, as analyzed with the case–crossover design. We observed that any concurrent use of benzodiazepines, antidepressants, or opioid analgesics with zolpidem showed no significant difference in suicidal risk than the use of zolpidem alone. Although the risk of suicide was 1.05-fold higher in cases taking the quadruple combination of benzodiazepines, antidepressants, and opioid analgesics with zolpidem than in those taking zolpidem alone, this result was not statistically significant (cOR, 1.05; 95% CI, 0.58–1.87). The sensitivity analysis of the case–crossover results, which was performed by varying hazard and control periods to 30 days, is shown in Table 2. The sensitivity analyses which were performed by varying the number of controls from five sets of control periods (main analyses) to two or three sets of control periods are shown in Supplementary Tables 3 and 4. The sensitivity analysis results were similar to the main analysis results.

Table 1 The risk of suicide in the individual with exposure to concurrent use of benzodiazepine, antidepressant, opioid analgesic with zolpidem from case–control study

Current exposure[a]	Cases[b] ($n=1928$)	Controls[b] ($n=18,404$)	Crude OR (95% CI)	Adjusted OR (95% CI)[c]
Time window 60 days				
Zolpidem only	24 (1.2)	54 (0.3)	1.00 (reference)	1.00 (reference)
Benzodiazepine and zolpidem	36 (1.9)	46 (0.2)	2.01 (1.03–3.92)	1.29 (0.64–2.61)
Antidepressant and zolpidem	7 (0.4)	10 (0.1)	1.68 (0.54–5.27)	0.89 (0.26–3.08)
Opioid analgesic and zolpidem	11 (0.6)	23 (0.1)	1.27 (0.52–3.11)	1.06 (0.42–2.70)
Benzodiazepine and antidepressant and zolpidem	93 (4.8)	26 (0.1)	7.76 (4.01–15.02)	2.80 (1.38–5.70)
Benzodiazepine and opioid analgesic and zolpidem	20 (1.0)	27 (0.1)	1.99 (0.90–4.36)	1.32 (0.58–3.01)
Antidepressant and opioid analgesic and zolpidem	2 (0.1)	4 (0.0)	1.50 (0.25–8.82)	1.39 (0.22–8.78)
Benzodiazepine and antidepressant and opioid analgesic and zolpidem	39 (2.0)	26 (0.1)	3.83 (1.87–7.85)	1.95 (0.91–4.16)
Time window 30 days				
Zolpidem only	29 (1.5)	47 (0.3)	1.00 (reference)	1.00 (reference)
Benzodiazepine and zolpidem	34 (1.8)	28 (0.2)	2.11 (1.04–4.29)	1.45 (0.68–3.09)
Antidepressant and zolpidem	5 (0.3)	7 (0.0)	1.26 (0.35–4.51)	0.73 (0.18–3.00)
Opioid analgesic and zolpidem	7 (0.4)	15 (0.1)	0.91 (0.32–2.58)	0.70 (0.24–2.05)
Benzodiazepine and antidepressant and zolpidem	79 (4.1)	22 (0.1)	5.61 (2.84–11.07)	2.03 (0.97–4.25)
Benzodiazepine and opioid analgesic and zolpidem	12 (0.6)	16 (0.1)	1.33 (0.53–3.33)	0.84 (0.32–2.21)
Antidepressant and opioid analgesic and zolpidem	1 (0.1)	2 (0.0)	1.01 (0.09–11.80)	1.22 (0.10–14.76)
Benzodiazepine and antidepressant and opioid analgesic and zolpidem	21 (1.1)	14 (0.1)	2.74 (1.17–6.42)	1.52 (0.60–3.85)

OR odds ratio, *CI* confidence interval

[a]At first, exposure categorized into 15 mutually exclusive groups according to the combination of benzodiazepine, antidepressant, opioid analgesic and zolpidem. Finally, only the results of the eight groups, including the zolpidem, were displayed for comparison

[b]Cases and controls were matched on age group, sex, index year, region, income level, and type of health insurance

[c]Adjusted for schizophrenic spectrum disorders, major depressive disorder, other type of depression, bipolar disorder, anxiety, substance use, other mental disorders, insomnia and Charlson comorbidity index (CCI)

Discussion

Our population-based case–control and case–crossover studies examined whether the concurrent use of benzodiazepines, antidepressants, and opioid analgesics with zolpidem resulted in a higher risk of suicide than the use of zolpidem alone. While the results of the case–control study revealed that the concurrent use of benzodiazepines and antidepressants with zolpidem was associated with an increased risk of suicide compared with the use of zolpidem alone (aOR, 2.80; 95% CI, 1.38–5.70), the case–crossover analysis found no significant difference in suicide risk between the concurrent use of benzodiazepine and antidepressant with zolpidem and the use of zolpidem alone (cOR, 0.92; 95% CI, 0.55–1.52). In the case–crossover design, time-invariant characteristics between individuals are eliminated, because each case serves as its own control. However, in the case–control design, there might be the residual confounding that has not been considered.

Another explanation for the differing results might be possible when considering the inherent characteristics of a case–crossover study, a design that was developed to assess acute events in association with short-term exposure and answer questions, such as "Was this event triggered by unusual exposure that happened just before?" [43] Our conflicting results might mean that the short-term concurrent use of medications is less relevant to the trigger of suicide, but that persons taking multiple medications may be at a higher risk of suicide than those who are not. The case–crossover study relies on the assumption that the exposure must be intermittent and its effects must be transient-holding [44]. However, it is possible that, in cases of frequent use of benzodiazepines, antidepressants, and opioid analgesic with zolpidem, neither the intermittency of exposure assumption nor the transiency of effect hold, which would violate the assumptions of case–crossover design.

Although comparisons to previous studies are not straightforward due to methodological differences, the present findings could still be indirectly compared with the findings of previous studies. The increased rate of suicide risk found with concurrent use is in concordance with the results of a study that found a higher risk of suicide attempt for co-users of alcohol and central nervous system (CNS) depressants (sedatives, anxiolytics, hypnotics, and opioids) (OR, 8.76; 95% CI, 1.02–75.44) than in sole users of CNS depressants (OR, 3.01; 95% CI, 1.09–8.31) or sole users

Table 2 Odds ratio for the risk of suicide in the individual with exposure to concurrent use of benzodiazepine, antidepressant, opioid analgesic with zolpidem from case–crossover analysis

Current exposure[a]	Exposed in hazard period[b] ($n=1803$)	Exposed in control period[b] ($n=9015$)	Crude OR (95% CI)
Time window 60 days			
Zolpidem only	31 (1.72)	80 (0.89)	1.00 (reference)
Benzodiazepine and zolpidem	53 (2.94)	150 (1.66)	0.91 (0.54–1.53)
Antidepressant and zolpidem	8 (0.44)	27 (0.30)	0.77 (0.31–1.86)
Opioid analgesic and zolpidem	5 (0.28)	27 (0.30)	0.48 (0.17–1.35)
Benzodiazepine and antidepressant and zolpidem	63 (3.49)	177 (1.96)	0.92 (0.55–1.52)
Benzodiazepine and opioid analgesic and zolpidem	15 (0.83)	48 (0.53)	0.81 (0.40–1.65)
Antidepressant and opioid analgesic and zolpidem	1 (0.06)	6 (0.07)	0.43 (0.05–3.72)
Benzodiazepine and antidepressant and opioid analgesic and zolpidem	32 (1.77)	79 (0.88)	1.05 (0.58–1.87)
Time window 30 days			
Zolpidem only	32 (1.77)	82 (0.91)	1.00 (reference)
Benzodiazepine and zolpidem	39 (2.16)	137 (1.52)	0.73 (0.42–1.25)
Antidepressant and zolpidem	8 (0.44)	29 (0.32)	0.71 (0.29–1.71)
Opioid analgesic and zolpidem	2 (0.11)	23 (0.26)	0.22 (0.05–1.00)
Benzodiazepine and antidepressant and zolpidem	54 (3.00)	208 (2.31)	0.67 (0.40–1.10)
Benzodiazepine and opioid analgesic and zolpidem	6 (0.33)	48 (0.53)	0.32 (0.13–0.82)
Antidepressant and opioid analgesic and zolpidem	0 (0.00)	7 (0.08)	–[c]
Benzodiazepine and antidepressant and opioid analgesic and zolpidem	11 (0.61)	61 (0.68)	0.46 (0.22–0.99)

OR odds ratio, *CI* confidence interval

[a]At first, exposure categorized into 15 mutually exclusive groups according to the combination of benzodiazepine, antidepressant, opioid analgesic and zolpidem. Finally, only the results of the eight groups, including the zolpidem, were displayed for comparison

[b]A single hazard period matched randomly with five sets of control period

[c]Not estimated due to the low observation

of alcohol (OR, 4.07; 95% CI, 2.06–8.02) [41]. Opposing reports also persist. Neutel et al. [45] found that risk of suicide attempt was higher in patients prescribed benzodiazepines without antidepressants (aOR, 6.2; 95% CI, 2.6–15.4) than in patients prescribed benzodiazepines with antidepressants (aOR, 2.4; 95% CI, 0.6–10.2). Fontanella et al. [46] found that the hazard of mortality in patients with schizophrenia was higher for those prescribed benzodiazepines without an antipsychotic (hazard ratio [HR], 3.08; 95% CI, 2.63–3.61; $P<0.001$) than for those prescribed benzodiazepines in combination with antipsychotics (HR, 1.48; 95% CI, 1.15–1.91; $P=0.002$).

Although the biological mechanism responsible for the possible association between increased suicide risk and concurrent use of zolpidem remains unclear, possible mechanisms may be explained. Benzodiazepines and zolpidem both induce sedation by enhancing the effect of GABA within the central nerve system [47]. The brains of individuals who died by suicide display altered expressions and regulations of genes involved in the γ-aminobutyric acid (GABA) ergic system [26–30]. Lee et al. [48] found that GABA concentrations in the cerebrospinal fluid were correlated with both impulsivity and prior suicidal behavior. Altered levels of serotonin and serotonin signaling in suicidal individuals have also been detected in multiple studies [31–33]. Concurrent use of central nerve system (CNS) depressants such as benzodiazepines, antidepressants, and opioid analgesics with zolpidem may increase the risk of suicide through the aforementioned neurotransmitter alternations that exert additive or perhaps synergic depressive effects. Our findings could be attributed to such neurotransmitter-modulating mechanisms.

Our study has several strengths. First, this is the first study to examine the risk of suicide associated with concurrent use of zolpidem, benzodiazepines, antidepressants, and opioid analgesics as well as the use of zolpidem alone. Second, our study used national, representative, population-based samples, and our exposure of interest were all reimbursed, prescription drugs from the health insurance body. Third, we conducted not only a matched case–control study after adjusting for comorbid psychiatric disorders as major confounders of suicide, but we also conducted a case–crossover analysis, which inherently adjusted for time-invariant confounders. The combination of both approaches may contribute to more reliable evidence in clinical practice.

However, limitations should be considered when interpreting the present findings. First, our study is based on the

claims database, and there is therefore potential inaccuracy for coding of suicide. Due to the strong social stigma in South Korea related to mental disorders and suicide, it is possible that many suicide attempts have not been reported to or claimed for the Korean NHIS program. If there were cases of suicide that were not recorded as such, we would not have captured all cases of suicide. However, there is no evidence that outcomes generally categorized into the controls. We assume that such non-differential misclassifications may be minimal due to relatively clear records for diagnosis of suicide [37]. Second, due to database limitations, we could not sufficiently consider the confounding by indication for the various severities and durations of each disease. Moreover, although substance use was considered, the concomitant use of alcohol as a strong confounding variable for suicide risk could not be assessed. However, these limitations could not affect our case–crossover study, which is a within-subject technique with each case serving as its own control, and likely only affected our case–control results minimally due to the evaluation of suicide risk as a comparison between concurrent use of zolpidem and use of zolpidem alone. Third, due to database limitations, we could not consider non-drug interventions, such as psychological counseling, that could affect suicide risk. Moreover, psychotropic drug dosages and use durations were not considered in our study. Fourth, because zolpidem is prescribed "on-demand", we could not accurately determine actual patient doses and durations. To overcome this limitation, we conducted various sensitivity analyses with varying time windows.

Health care professionals may expect benzodiazepines, antidepressants, and opioid analgesics to protect against suicide by reducing insomnia, anxiety, and chronic pain, three modifiable risk factors for suicide [8, 49–51]. Although they require more specific elaboration, these results demonstrate that a careful understanding of clinical factors and mechanisms associated with zolpidem and suicide risk is needed when physicians prescribe zolpidem to concurrent users of benzodiazepines, antidepressants, and opioid analgesic. This is important for the development of future treatment options and prevention of suicide. The preparation of evidence-based treatment guidelines, practical strategies and public policies is required for the more prudent use of these drugs in clinical practice as well.

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Compliance with ethical standards

Conflict of interest The Seockchun Research Fund was not involved in the current study. The authors declare no competing interests, including specific financial interests, relationships, or affiliations, relevant to the subject of this manuscript.

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