# Antipsychotic Discontinuation and Suicide in Schizophrenia Patients A Nested Case-Control Study

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# Abstract

*Background* Schizophrenia patients have shorter life expectancy relative to that of the general population, and their suicide risk is reportedly higher. Although antipsychotic discontinuation rates are high, antipsychotic treatment has been associated with lower suicide mortality, and patients who do not use antipsychotics are at greater risk of suicide relative to those who use the medication. Furthermore, maintenance treatment with antipsychotic drugs protects schizophrenia patients from relapse. However, little is known about antipsychotic discontinuation, suicide risk, or the time during which suicide risk is highest following antipsychotic discontinuation. Therefore, this study investigated whether discontinuity of antipsychotics is associated with suicide in schizophrenia patients.

*Methods* A population-based nested case-control study was conducted using the Korean National Health Insurance claims database (2002-2013). From the study population of 7,519 patients with the diagnosis of schizophrenia and at least one antipsychotics described, we identified 154 suicide cases and 760 matched controls. We calculated the days after last prescribed medication so that discontinuity of antipsychotics was defined. Conditional logistic regression were used to examine the association between discontinuity of antipsychotics and suicide adjusting for possible confounding covariates.

*Results* Suicide risk was particularly high during the first thirty days after discharge after stopping antipsychotics compared with current user after adjusting all covariates (AOR: 4.667, 95% CI: 2.425–8.984).

*Conclusion* Maintenance treatment with antipsychotics could help to reduce suicide risk. The results indicated that there is a need to monitor schizophrenia patients following antipsychotic discontinuation.


# Background

Suicide is considered a major public health challenge and one of the leading causes of loss of life years worldwide.[1] Of the Organization for Economic Co-operation and Development(OECD) countries, South Korea has the highest suicide rate.[2] Over the past two decades, suicide rates have continued to increase in South Korea, peaking in 2010, and suicide is now the fourth leading cause of death.[3] Schizophrenia patients have shorter life expectancy relative to that of the general population, and their suicide risk is reportedly 12 times higher.[4] Lifetime suicide rates have been estimated at 5% in schizophrenia patients in various settings.[5, 6] As schizophrenia is associated with increased suicide risk, it is important for researchers and clinicians to detect suicide risk factors, to aid suicide prevention.

Previous epidemiological and clinical studies have examined suicide predictors and risk factors, which include multiple psychiatric admissions, previous suicide attempts, mood disorders, drug misuse, and poor medication treatment.[7, 8] Antipsychotic discontinuation rates are high at 74% at 18 months for chronic schizophrenia,[9] 42% at 12 months for first-episode schizophrenia in Europe,[10] and 46% for continued treatment during the 30 days following first discharge in Finland.[11] Nonetheless, the role of

pharmacotherapy is the top priority in treating schizophrenia patients. Although suicide risk reduction depends on the type of antipsychotic used, and second-generation antipsychotics are more likely to reduce suicide risk relative to first-generation antipsychotics, antipsychotic treatment has been associated with lower suicide mortality,[12] and patients who do not use antipsychotics are at greater risk of suicide relative to those who use the medication.[13] Furthermore, maintenance treatment with antipsychotic drugs protects schizophrenia patients from relapse.[14] However, little is known about antipsychotic discontinuation, suicide risk, or the time during which suicide risk is highest following antipsychotic discontinuation. Therefore, we conducted a nested case-control study to examine the association between antipsychotic discontinuation and suicide risk via nationwide sampling of claims data.

## Methods

# Data and Subjects

All Korean citizens are obligated to enroll in the single-payer, national health insurance and medical aid program administered by the National Health Insurance Corporation. Data were acquired from the National Health Insurance Service-National Sample Cohort (NHIS-NSC), which included 1,025,340 representative subjects (approximately 2.2% of the population), who were randomly stratified and selected based on age, sex, insurance type, income, residential region, and individual total medical costs. The database includes information regarding patients' unique de-identification numbers, age, sex, insurance type, diagnosis according to the International Classification of Diseases (ICD-10), medical costs, and prescribed drugs. In addition, these numbers are linked to mortality information from the Korean National Statistical Office. Details of the NHIS-NSC database are provided in a previous report.[15]

Of the 1,025,340 enrollees, we identified a cohort of 7,519 patients diagnosed with primary or secondary schizophrenia (ICD-10 codes F20.x) for the first time and treated with at least one antipsychotic medication during the same visit, between 2002 and 2013. We included all antipsychotics prescribed between 2002 and 2013, with the exception lithium, according the Anatomical Therapeutic Chemical (ATC) code group N05A.[16] We also included atypical antipsychotics approved for schizophrenia treatment in Korea (zotepine, molindone, nemonapride, and blonanserin). Patients using antipsychotics were observed from the date of first prescription to follow-up loss (emigration or disqualification from national health insurance), death (whether by suicide or any other cause), or December 31, 2013, whichever occurred first.

In this nested case-control study using risk-set sampling, control patients were selected from the cohort of patients who used antipsychotics and were at risk of suicide upon recruitment. Each control subject was required to be alive at the time of the corresponding patient's suicide. The index date was defined as the date upon which suicide occurred. Control patients were randomly extracted from the case-risk set at a suicide-to-control ratio of up to 1:5 after they had been matched to a corresponding patient group according to sex and 5-year interval age in 2002 and at the time of schizophrenia diagnosis. We identified 154 cases involving individuals who had committed suicide (ICD-10 codes X60-X84). Control subjects

were matched to 144 and 10 of the individuals who committed suicide at suicide-to-control ratios of 1:5 (n = 720) and 1:4 (n = 40), respectively (Fig. 1).

# Time since antipsychotic discontinuation (days)

To identify the time at which schizophrenia patients were at the greatest risk of suicide following discontinuation of antipsychotic medication, we defined time since antipsychotic discontinuation as follows (Supplementary Fig. 1): We defined the date of antipsychotic discontinuation as the last date for which medication was prescribed, which was calculated by counting the number of days' supply from the date of the final prescription. We then calculated the number of days between the antipsychotic discontinuation and index dates as the number of days since antipsychotic discontinuation. Use of antipsychotic medication was classified as follows: current use (until the index date) or 30, 31–90, 91–180, 181–365, or > 365 days since antipsychotic discontinuation. In addition, we included individuals who had been visited or admitted to clinics/hospital for psychiatric problems (diagnosis code F20) subsequent to antipsychotic discontinuation, to determine whether the withdrawal of antipsychotic medication was planned or sudden. While medical practice and the dispensation of medication generally occur separately in Korea, prescriptions for psychiatric medication are filled in psychiatric clinics/hospitals; therefore, prescriptions for antipsychotics are always filled on the date on which they are produced. The aim of this policy is to relieve mental stress in schizophrenia patients and avoid social stigma in Korea. Therefore, the use of the date of antipsychotic discontinuation, calculated as described above, and the index date to calculate the number of days since antipsychotic discontinuation provided as accurate a reflection of this period as possible.

# Covariates

All covariates were assessed using information available before or on the index date. Sociodemographic and clinical risk factors for suicide were included in the analysis. Sociodemographic factors included sex, age (16–29, 30–39, 40–49, 50–59, 60–69, and ≥ 70 years), region (urban or rural), and household income (medical aid and income quintiles Q1 [low] to Q5 [high]) on the index date. We used the average monthly insurance premium as a proxy for household income. In Korea, individuals qualify for medical aid if their household income is below $600 per month; otherwise, they qualify for national health insurance. Individuals enrolled in the national health insurance program were distributed between the 1st and 100th income percentiles, while those who received medical aid were classified at the zero percentile. We classified household income as follows: medical aid and income quintiles Q1 (< 20%), Q2 mid-low (21–40%), Q3 (41–60%), Q4 (61–80%), and Q5 (> 80%).

To account for patients' symptom severity, we included levels of mental disability (according to disabled person welfare law), which was assessed using Global Assessment Function (GAF), as follows: none, moderate (GAF score 51–60), and severe (GAF score < 50). Comorbidity was assessed using The Charlson comorbidity index, which was calculated by reviewing patients' medical history from the beginning of the study period until the index date.[17] Underlying diagnoses related to psychiatric disorders

included sleep (F5, G47), mood (F30–F34, F38–F39), and anxiety and stress disorders (F4) and substance abuse (F1).

We included the following possible suicide predictors: emergency department visits (none, one or more) during the year preceding the index date as a proxy for suicide attempts and the number of admissions for psychiatric problems other than dementia, as strong risk factors for suicide.

We defined continuity of care as longitudinal continuity, calculated using the Continuity of Care (COC) index, which measures how often a patient has consulted the same psychiatrist over a given period.[18] The formula for the COC index is as follows:

$$\mathrm{COC} = \frac{\left[\left(\sum_{j=1}^{m} n_j^2\right) - N\right]}{N(N-1)}$$

where $N$ is the total number of psychiatric outpatient visits; $n_j$ is the number of visits to the $j$th provider; and $m$ is the number of available providers. Index values ranged from 0 to 1, where 0 and 1 indicated no and perfect continuity, respectively. Psychiatric outpatient visits for problems other than dementia were included in the COC calculation. A minimum of three psychiatric outpatient visits was mandatory for a valid COC score for a particular time frame, because continuity remains invalid with a limited number of visits. We included patients with ≤ 3 psychiatric outpatient visits as a separate group (“no-index group”). Excluding them could have biased the results, because this group can exhibit unique characteristics. Moreover, because they represented the largest group in our data, excluding these individuals from the analysis was inappropriate.

We estimated medication adherence via the “proportion of days covered,”[19] which is the number of days on which patients have access to a drug within a specified period. The date on which an antipsychotic medication prescription was first filled was used as the beginning of the patient’s review period. The date of disenrollment or final measurement was used as the index date. We also included the number of different types of antipsychotic medication prescribed during follow up.

# Statistical analysis

Descriptive statistics were used to describe clinical and demographic variables for the suicide and control groups. As the groups were matched according to age, sex, and schizophrenia diagnosis date, these measures did not differ significantly between them. Conditional logistic regression was conducted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) to assess the association between antipsychotic discontinuation and suicide risk. A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SAS software package (ver. 9.4; SAS Institute, Cary, NC, USA).

# Results

Table 1 shows the general characteristics of the suicide and control groups. The total case-control sample included 914 patients diagnosed with schizophrenia between 2002 and 2013. Each control subject (n = 760) was matched with up to 5 individuals who had committed suicide (n = 154). Matching variables, including age, sex, and year of schizophrenia diagnosis were distributed evenly between groups. Most patients (51.2%) were younger than 40 years of age. The suicide group was more likely to have discontinued antipsychotics relative to the control group (70.1% vs. 60.4%). The average number of days since last prescription did not differ significantly between the suicide (24.8; SD 16.2) and control (26.1; SD 16.9) groups (P = 0.370). The proportion of schizophrenia patients with medical aid in the suicide group (18.8%) was higher relative to that of the control group (15.4%). The suicide group was more likely to have related mental health conditions: 39.0%, 48.1%, 39.6%, and 11.0% with sleep disorders, mood disorders, stress-related disorders, and substance abuse, respectively. The suicide group was also more likely to have had multiple admissions for psychiatric problems (> 2 admissions: 28.6% vs 16.1%) and used emergency departments during the preceding year relative to the control group (18.2% vs 7.2%).

Table 1

Characteristics of the suicide and control groups

| Variable | n | % | Suicide cases | | Controls | |
|---|---|---|---|---|---|---|
| | | | n | % | n | % |
| **Total** | 914 | | 154 | 16.8 | 760 | 83.2 |
| **Sex*** | | | | | | |
| Male | 526 | 57.5 | 89 | 57.8 | 437 | 57.5 |
| Female | 388 | 42.5 | 65 | 42.2 | 323 | 42.5 |
| **Age*** | | | | | | |
| 16-29 | 202 | 22.1 | 33 | 21.4 | 169 | 22.2 |
| 30-39 | 266 | 29.1 | 46 | 29.9 | 220 | 28.9 |
| 40-49 | 175 | 19.1 | 29 | 18.8 | 146 | 19.2 |
| 50-59 | 104 | 11.4 | 19 | 12.3 | 85 | 11.2 |
| 60-69 | 94 | 10.3 | 18 | 11.7 | 76 | 10.0 |
| 70- | 73 | 8.0 | 9 | 5.8 | 64 | 8.4 |
| **Index year*** | | | | | | |
| 2002-2004 | 88 | 9.6 | 12 | 7.8 | 76 | 10.0 |
| 2005-2007 | 247 | 27.0 | 48 | 31.2 | 199 | 26.2 |
| 2008-2010 | 308 | 33.7 | 55 | 35.7 | 253 | 33.3 |
| 2011-2013 | 271 | 29.6 | 39 | 25.3 | 232 | 30.5 |
| **Days after stopping antipsychotics** | | | | | | |
| Current use | 300 | 32.8 | 33 | 21.4 | 267 | 35.1 |
| 1 - 30 days | 94 | 10.3 | 29 | 18.8 | 65 | 8.6 |
| 31 - 90 days | 48 | 5.3 | 11 | 7.1 | 37 | 4.9 |
| 91 - 180 days | 44 | 4.8 | 7 | 4.5 | 37 | 4.9 |
| 181 - 365 days | 76 | 8.3 | 16 | 10.4 | 60 | 7.9 |
| > 365 days | 305 | 33.4 | 45 | 29.2 | 260 | 34.2 |
| Others** | 47 | 5.1 | 13 | 8.4 | 34 | 4.5 |
| **Income** | | | | | | |
| Medical aid | 146 | 16.0 | 29 | **18.8** | 117 | 15.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Q1(Low) | 129 | 14.1 | 16 | 10.4 | 113 | 14.9 |
| Q2 | 135 | 14.8 | 21 | 13.6 | 114 | 15.0 |
| Q3 | 143 | 15.6 | 23 | 14.9 | 120 | 15.8 |
| Q4 | 143 | 15.6 | 27 | 17.5 | 116 | 15.3 |
| Q5(High) | 218 | 23.9 | 38 | 24.7 | 180 | 23.7 |
| **City** | | | | | | |
| Rural | 297 | 32.5 | 57 | **37.0** | 240 | 31.6 |
| Urban | 617 | 67.5 | 97 | 63.0 | 520 | 68.4 |
| **Mental disability** | | | | | | |
| None | 754 | 82.5 | 126 | 81.8 | 628 | 82.6 |
| Mild | 51 | 5.6 | 14 | **9.1** | 37 | 4.9 |
| Severe | 109 | 11.9 | 14 | 9.1 | 95 | 12.5 |
| **Charlson's comorbidity index** | | | | | | |
| 0 | 532 | 58.2 | 88 | 57.1 | 444 | 58.4 |
| 1 | 211 | 23.1 | 39 | 25.3 | 172 | 22.6 |
| 2 | 79 | 8.6 | 11 | 7.1 | 68 | 8.9 |
| ≥3 | 92 | 10.1 | 16 | 10.4 | 76 | 10.0 |
| **Sleep disorders** | | | | | | |
| No | 677 | 74.1 | 94 | 61.0 | 583 | 76.7 |
| Yes | 237 | 25.9 | 60 | **39.0** | 177 | 23.3 |
| **Mood disorders** | | | | | | |
| No | 585 | 64.0 | 80 | 51.9 | 505 | 66.4 |
| Yes | 329 | 36.0 | 74 | **48.1** | 255 | 33.6 |
| **Stress related disorders** | | | | | | |
| No | 629 | 68.8 | 93 | 60.4 | 536 | 70.5 |
| Yes | 285 | 31.2 | 61 | **39.6** | 224 | 29.5 |
| **Substance abuse** | | | | | | |
| No | 854 | 93.4 | 137 | 89.0 | 717 | 94.3 |
| Yes | 60 | 6.6 | 17 | **11.0** | 43 | 5.7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **No. of psychiatric admissions** | | | | | | |
| 0 | 498 | 54.5 | 67 | 43.5 | 431 | 56.7 |
| 1 | 250 | 27.4 | 43 | 27.9 | 207 | 27.2 |
| 2 | 87 | 9.5 | 24 | **15.6** | 63 | 8.3 |
| ≥3 | 79 | 8.6 | 20 | **13.0** | 59 | 7.8 |
| **ED visits within a year** | | | | | | |
| None | 831 | 90.9 | 126 | 81.8 | 705 | 92.8 |
| One or more | 83 | 9.1 | 28 | 18.2 | 55 | 7.2 |
| **Continuity of care index** | | | | | | |
| Total visits≤3 | 175 | 19.1 | 21 | 13.6 | 154 | 20.3 |
| <1 | 389 | 42.6 | 82 | 53.2 | 307 | 40.4 |
| 1 | 350 | 38.3 | 51 | 33.1 | 299 | 39.3 |
| **Medication compliance** | | | | | | |
| <0.8 | 688 | 75.3 | 120 | 77.9 | 568 | 74.7 |
| ≥0.8 | 226 | 24.7 | 34 | 22.1 | 192 | 25.3 |
| **No. of antipsychotics** | | | | | | |
| 1 | 415 | 45.4 | 56 | 36.4 | 359 | 47.2 |
| 2 | 226 | 24.7 | 37 | 24.0 | 189 | 24.9 |
| ≥3 | 273 | 29.9 | 61 | 39.6 | 212 | 27.9 |

The index date was defined as the date of suicide occur.

*Matching variables.

**Others: those who used medical resources for mental disorders subsequent to antipsychotic discontinuation

Table 2 shows the results of both the crude and adjusted conditional logistic regression analyses for the suicide group. In the crude model, suicide risk in schizophrenia patients with mental disorders (e.g., sleep disorders, mood disorder, stress related disorders, and substance abuse), multiple psychiatric admissions, poor continuity of care, and polypharmacy involving antipsychotics was greater relative to that in other subjects. However, adjusted odds ratios (AORs) for suicide risk in patients with sleep disorders (AOR: 2.500 95% CI: 1.599–3.910) and emergency department visits during the preceding year (AOR: 2.590, 95% CI: 1.418–4.732) were significantly higher relative to those for other subjects. Suicide risk in

schizophrenia patients who had discontinued antipsychotic medication for 30 days was greater relative to that of current users, after adjusting all covariates (AOR: 4.667, 95% CI: 2.425–8.984).

Table 2
Results of conditional logistic regression, showing odds ratios for suicide

| Variable | cOR | 95% CI | | aOR | 95% CI | |
|---|---|---|---|---|---|---|
| **Days after stopping antipsychotics** | | | | | | |
| Current use | 1.000 | | | 1.000 | | |
| 1–30 days | **4.031** | **2.216** | **7.333** | **4.667** | **2.425** | **8.984** |
| 31–90 days | **2.458** | **1.113** | **5.430** | 2.132 | 0.881 | 5.157 |
| 91–180 days | 1.659 | 0.623 | 4.420 | 1.983 | 0.675 | 5.820 |
| 181–365 days | **2.204** | **1.060** | **4.587** | 1.868 | 0.802 | 4.352 |
| > 365 days | 1.291 | 0.773 | 2.154 | 1.518 | 0.805 | 2.865 |
| Others* | **2.825** | **1.334** | **5.987** | 2.296 | 1.000 | 5.270 |
| **Income** | | | | | | |
| Medical aid | 1.213 | 0.687 | 2.141 | 2.087 | 0.991 | 4.394 |
| Q1(Low) | 0.684 | 0.364 | 1.288 | 0.890 | 0.442 | 1.792 |
| Q2 | 0.864 | 0.474 | 1.575 | 0.940 | 0.476 | 1.855 |
| Q3 | 0.914 | 0.519 | 1.610 | 0.988 | 0.525 | 1.860 |
| Q4 | 1.107 | 0.637 | 1.925 | 1.333 | 0.714 | 2.486 |
| Q5(High) | 1.000 | | | 1.000 | | |
| **City** | | | | | | |
| Rural | 1.000 | | | 1.000 | | |
| Urban | 1.272 | 0.890 | 1.820 | 1.253 | 0.839 | 1.873 |
| **Mental disability** | | | | | | |
| None | 1.000 | | | 1.000 | | |
| Moderate | 1.843 | 0.972 | 3.496 | 1.500 | 0.722 | 3.114 |
| Severe | 0.741 | 0.404 | 1.360 | 0.598 | 0.294 | 1.214 |
| **Charlson's comorbidity index** | | | | | | |
| 0 | 1.000 | | | 1.000 | | |

cOR: crude odds ratio; CI: confidence interval; aOR: adjusted odds ratio

*Others: those who used medical resources for mental disorders subsequent to antipsychotic discontinuation

| Variable | cOR | 95% CI | | aOR | 95% CI | |
|---|---|---|---|---|---|---|
| 1 | 1.150 | 0.745 | 1.775 | 0.975 | 0.596 | 1.595 |
| 2 | 0.809 | 0.397 | 1.647 | 0.718 | 0.326 | 1.583 |
| ≥ 3 | 1.083 | 0.554 | 2.115 | 0.868 | 0.416 | 1.812 |
| **Sleep disorders** | | | | | | |
| No | 1.000 | | | 1.000 | | |
| Yes | **2.281** | **1.548** | **3.360** | **2.500** | **1.599** | **3.910** |
| **Mood disorders** | | | | | | |
| No | 1.000 | | | 1.000 | | |
| Yes | **1.977** | **1.362** | **2.868** | 1.425 | 0.899 | 2.261 |
| **Stress related disorders** | | | | | | |
| No | 1.000 | | | 1.000 | | |
| Yes | **1.617** | **1.114** | **2.346** | 1.146 | 0.737 | 1.783 |
| **Substance abuse** | | | | | | |
| No | 1.000 | | | 1.000 | | |
| Yes | **2.120** | **1.150** | **3.911** | 1.568 | 0.782 | 3.142 |
| **No. of psychiatric admissions** | | | | | | |
| 0 | 1.000 | | | 1.000 | | |
| 1 | 1.324 | 0.864 | 2.029 | 0.949 | 0.575 | 1.567 |
| 2 | **2.651** | **1.498** | **4.690** | 1.890 | 0.953 | 3.750 |
| ≥ 3 | **2.407** | **1.306** | **4.435** | 1.420 | 0.680 | 2.966 |
| **ED visit within a year** | | | | | | |
| None | 1.000 | | | 1.000 | | |
| One or more | **3.134** | **1.848** | **5.314** | **2.590** | **1.418** | **4.732** |
| **Continuity of care index** | | | | | | |
| Total visits ≤ 3 | 0.714 | 0.398 | 1.279 | 0.751 | 0.380 | 1.482 |

cOR: crude odds ratio; CI: confidence interval; aOR: adjusted odds ratio

*Others: those who used medical resources for mental disorders subsequent to antipsychotic discontinuation

| Variable | cOR | 95% CI | | aOR | 95% CI | |
|---|---|---|---|---|---|---|
| < 1 | **1.644** | **1.107** | **2.442** | 1.130 | 0.698 | 1.832 |
| 1 | 1.000 | | | 1.000 | | |
| **Medication compliance** | | | | | | |
| < 0.8 | 1.000 | | | 1.000 | | |
| ≥ 0.8 | 0.833 | 0.549 | 1.263 | 1.229 | 0.748 | 2.020 |
| **No. of antipsychotics** | | | | | | |
| 1 | 1.000 | | | 1.000 | | |
| 2 | 1.300 | 0.820 | 2.062 | 1.324 | 0.779 | 2.252 |
| ≥ 3 | **2.033** | **1.314** | **3.147** | 1.589 | 0.900 | 2.806 |
| cOR: crude odds ratio; CI: confidence interval; aOR: adjusted odds ratio | | | | | | |
| *Others: those who used medical resources for mental disorders subsequent to antipsychotic discontinuation | | | | | | |

# Discussion

In this nested case-control study, we examined the association between antipsychotic discontinuation and suicide in schizophrenia patients, using data from the NHIS-NSC. Suicide risk in those who had discontinued antipsychotics for 30 days was greater relative to that observed in current users. In addition, schizophrenia patients who received medical aid were at greater suicide risk relative to other subjects, after controlling for covariates. Crude odds ratios in schizophrenia patients with moderate mental disability, sleep disorders, mood disorders, stress-related disorders, or substance abuse were higher relative to those observed in other subjects. Moreover, multiple psychiatric admissions, use of multiple types of antipsychotic medication, emergency department visits during the preceding year, and poor continuity of care related to psychiatric disorders predicted suicide in patients using antipsychotic medication.

Our findings are consistent with those of other studies examining the relationship between antipsychotic discontinuation and outcome measures, such as relapse, suicide attempts, and suicide-related mortality, in other populations. A Finnish observational high-risk cohort study involving hospitalized schizophrenia patients with a history of at least one suicide attempt showed that current use of any antipsychotic medication was associated with lower suicide-related mortality relative to that observed for previous use.[12] A large cohort study conducted by Walker et al. suggested that suicide incidence in schizophrenia patients who had discontinued clozapine was higher relative to that of those who currently used antipsychotics.[20] A study involving schizophrenia patients aged 15–45 years, who had been prescribed olanzapine or risperidone for at least 90 days suggested that those who did not have prescriptions for

antipsychotics filled on time were more likely to commit suicide relative to those who had prescriptions filled promptly.[21] A five-year observational study involving patients with first-episode psychosis indicated that ceasing antipsychotic medication increased first-relapse rate almost fivefold, and the cumulative rates second- and third-relapse rate, relative to those observed with continued treatment.[14] These findings indicated that cessation of drug therapy increased the incidence of repeated relapse, which could increase suicide risk.

There could be an explanation for the finding that suicide risk increased in schizophrenia patients who discontinued antipsychotic medication. One possible explanation for our findings is that schizophrenia patients acknowledged their psychosis-related conditions following treatment during the acute phase of psychotic illness. They might have experienced simultaneous depressive symptoms, which could have increased the risk of suicide during the high-risk period. Another explanation could be that the results occurred because of schizophrenia patients' characteristics or the severity of mental health disorders, such as depression, stress, and substance abuse, rather than a direct causal effect of antipsychotics; however, irrespective of the reason for the increased risk, these patients require particularly close monitoring during treatment and shortly after cessation of antipsychotic medication. Furthermore, poor patients in particular received limited social support from others such as friends, family, or colleagues.[22] Because of this lack of support, these patients could be vulnerable when using medication and fail to take it on time.

This study has clinical and political implications. Our results showed that suicide risk increased within the first 30 days of antipsychotic discontinuation; therefore, physicians and family members should pay greater attention to the need for continuous monitoring of schizophrenia patients after planned withdrawal of antipsychotic medication or when unplanned or sudden withdrawal is indicated. Furthermore, a specific methodology should be followed for suicide prevention in schizophrenia patients. Regular assessment and evaluation of suicide risk is necessary in clinical practice. In addition, development of a plan for suicide prevention during hospitalization and care should include deep observation. Following discharge, it is advisable to establish a concrete plan for managing unexpected behavior. In particular, patients recently discharged from hospital or admitted to hospital repeatedly should be observed, to ensure that in times of personal crisis, involving significant environmental changes, high levels of stress, and severe depression, schizophrenia patients or their family members arrange frequent outpatient visits. In addition, relevant risk factors, such as social isolation, substance abuse, and depression, should be removed to prevent suicide.

The strengths of this study were the population-based design and the acquisition of data from the NHIS-NSC, which is representative of the entire country. In addition, follow up was robust because of our use of unique personal identification numbers for Korean residents, which were linked to the national mortality database. Recall bias was not an issue, as we used data from prescriptions for antipsychotic medication, which were recorded prior to the occurrence of the outcomes. Despite these strengths, several limitations should be considered. First, as with other studies that used administrative claims data, there were some potentially key covariates that we were unable to identify, such as previous family suicide attempts,

family structure, marital status, employment status, and previous suicide attempts. In addition, patients' histories of self-harm, including drug overdose, poisoning, self-laceration, and non-fatal suicide attempts prior to entry into the study, were unknown. Second, there are some issues to consider when using administrative claims data. Reliance on ICD-10 codes for comorbidity could lead to misclassification due to activities such as miscoding behavior. Third, the study could have been subject to certain inherent limitations caused by the use of administrative data, which lack information on schizophrenia subtypes. Fourth, as the data source was a claim dataset, actual medication adherence rates were not reflected in the data.

# Conclusion

The results provided further evidence of a relationship between antipsychotic discontinuation and suicide in schizophrenia patients using antipsychotics and relied on nationally representative cohort data. Our findings indicate that suicide risk is greatest 30 days after cessation of antipsychotic medication. Therefore, there is a need to monitor schizophrenia patients after withdrawal of antipsychotic medication is planned or when unplanned or sudden withdrawal is indicated.

# Abbreviations

OECD: the Organization for Economic Co-operation and Development; NHIS-NSC: the National Health Insurance Service-National Sample Cohort; ICD-10: the International Classification of Diseases; ATC: Anatomical Therapeutic Chemical; GAF: Global Assessment Function; COC: Continuity of Care; ORs: Odds Ratios; CIs: Confidence Intervals; SD: Standard Deviation; AORs: Adjusted Odds Ratios

# Declarations

### Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. This study was reviewed and approved by the ethical review board at the Graduate School of Public Health in Yonsei University. The requirement for informed consent was waived as the study was based on routinely collected administrative and claims data and the database was constructed after anonymization according to strict confidentiality guidelines.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets analyzed during the current study are not publicly available.

### Competing interests

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.


### Funding

Not applicable


### Authors' contributions

YC designed the study, analyzed the data, and wrote the draft. YC and ECP performed the literature review and interpretation for data analysis. All authors read and approved the final manuscript.


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# Figures

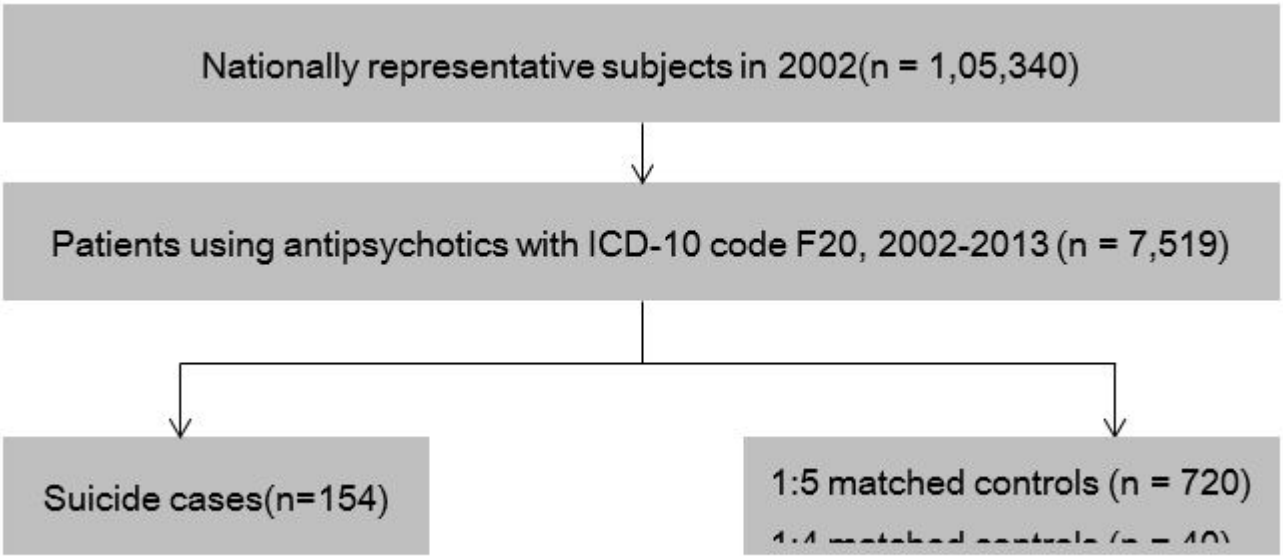


**Figure 1**

Flow chart for subject recruitment

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