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*Regular Article*

# Antipsychotic drugs and risk of newly diagnosed tuberculosis in schizophrenia

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*Aim:* Patients with schizophrenia have a higher incidence of tuberculosis than do people in the general population. Information is limited regarding the association between antipsychotic agents and the risk of tuberculosis in patients with schizophrenia. This exploratory study assessed the risk of tuberculosis among patients with schizophrenia on antipsychotic therapy.

*Methods:* Among a nationwide schizophrenia cohort derived from the National Health Insurance Research Database in Taiwan ($n$ = 32 399), we identified 284 patients who had developed newly diagnosed tuberculosis after their first psychiatric admission. Ten or fewer matched controls were selected randomly from the cohort for each patient based on risk-set sampling. We categorized exposure to antipsychotic medications by type and defined daily dose. Using multivariate methods, we explored individual antipsychotic agents for the risk of tuberculosis and employed a propensity-scoring method in sensitivity analyses to validate any associations.

*Results:* Among the antipsychotic agents studied and after adjustment for covariates, current use of clozapine was the only antipsychotic agent associated with a 63% increased risk of tuberculosis (adjusted risk ratio = 1.63, $P$ = 0.014). In addition, the association did not show a clear dose-dependent relationship. Clozapine combined with other antipsychotic agents showed a potential synergistic risk for tuberculosis (adjusted risk ratio = 2.30, $P$ = 0.044).

*Conclusion:* This exploratory study suggests the potential risk of clozapine on the risk of tuberculosis, especially for those on clozapine in combination with other antipsychotics. Future studies are needed to verify the association.

**Key words:** antipsychotics, clozapine, schizophrenia, tuberculosis.

TUBERCULOSIS IS CAUSED by infection with the acid-fast bacillus *Mycobacterium tuberculosis* and is a global health problem. In 2012, an estimated 8.6 million people developed tuberculosis, and 1.3 million died from the disease, which is nearly as many deaths as those caused by HIV infection.[1] Schizophrenia is the most deteriorating mental illness. In addition, schizophrenia patients are more prone to several medical comorbidities than the general population, including metabolic syndrome,[2] pneumonia,[3] and tuberculosis.[4] A recent study in Taiwan[4] reported a higher incidence of

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tuberculosis in patients with schizophrenia than in the general population. Understanding the risk factors for tuberculosis among schizophrenia patients would improve the quality of their care.

Patients with weak immune systems are vulnerable to tuberculosis. A number of diseases and medications weaken the immune system, such as HIV, diabetes mellitus, cancer, malnutrition, and immunomodulating drugs (e.g., cancer chemotherapeutics and transplantation antirejection drugs). Antipsychotics, the drugs often used to treat schizophrenia patients, carry an elevated risk for pneumonia, which is also an infectious disease.[3,5] In a prior study,[3] we reported that several antipsychotic agents increased the risk of incident pneumonia; clozapine carries the highest risk for pneumonia, then olanzapine, quetiapine, zotepine, and risperidone. The identified antipsychotics associated with the risk of pneumonia (such as clozapine and olanzapine) have high affinities for the histaminergic-1 (H1) receptor and the muscarinic-1 (M1) receptor. Regarding the neurobiological explanations, the possible mechanisms based on the affinities of neurotransmitter receptors could mediate the association between antipsychotics and pneumonia. Thus, whether the antipsychotics with high affinities for such transmitter receptors are associated with risk of tuberculosis deserves investigation.

Additionally, prior studies have shown that an infectious protozoan (i.e., *Toxoplasma gondii*) has been associated with schizophrenia. As for the psychopathological hypothesis, the studies[6,7] suggest that this protozoan may lead to more severe positive psychopathology in patients with schizophrenia.[7] The mechanism could be through the modulation of secretion or the effects of some neurotransmitters, such as dopamine or serotonin.[6] Studies investigating the association between psychopathological factors and the risk of tuberculosis are needed.

Antipsychotic treatment modifies several cytokines, and antipsychotics have immunosuppressive and anti-inflammatory effects.[8] Therefore, we hypothesize that the immune-modulating effects of antipsychotic agents influence host immune response to tuberculosis, which then leads to an increase in the prevalence of tuberculosis among schizophrenia patients. The association between antipsychotic agents and tuberculosis is not well documented in the medical literature. For instance, one study reported two cases in which patients were treated with clozapine and subsequently developed pulmonary tuberculosis.[9] However, we found no study using large-scale systematic datasets to explore the associations between individual antipsychotic agents and tuberculosis.

Accordingly, we designed a nested case–control study, derived from a large nationwide schizophrenia cohort in Taiwan, to investigate the clinical factors and antipsychotics exposure on the risk of tuberculosis among schizophrenia patients. We focused on the most commonly used individual antipsychotics for the therapy of schizophrenia patients in Taiwan to determine the risk of developing tuberculosis by employing multivariate methods and sensitivity analysis. This study estimates the risk for tuberculosis associated with antipsychotics in several dimensions, including temporal relations, dose-dependent relations, and combination therapies.

## METHODS

### Study subjects

The dataset source used in this study is described in more detail elsewhere[3,10] and is briefly summarized here. The single-payer National Health Insurance program was implemented in Taiwan in 1995, and coverage of the 23 million Taiwanese had reached 98% by the end of 2007. Data in the National Health Insurance Research Database (NHIRD) that could be used to identify enrollees or care providers were scrambled by the National Health Research Institutes and then made available for research use (http://w3.nhri.org.tw/nhird/en/Data_Protection.html).

The NHIRD is comprised of standard claims documents of the beneficiaries, including demographics, prescriptions, and expenditures for health-care providers. This study conformed to the Declaration of Helsinki. The Taipei City Hospital Review Board of the Committee on Human Subject Research approved this study. A waiver of informed consent was granted due to the minimal risk to the privacy of individual subjects, as the patient information had been de-identified before the analysis. All investigators signed an agreement guaranteeing patient confidentiality before using the database.

We used a subset of the NHIRD, the National Psychiatric Inpatient Medical Claims Database, that comprised a cohort of patients hospitalized for any psychiatric disorder (ICD-9-CM codes 290.xx to

319.xx) between 1996 and 2008 ($N$ = 187 117). We selected patients with at least one psychiatric hospital admission between 2000 and 2008 but no psychiatric admissions between 1996 and 1999 ($n$ = 125 225) from the database. We defined the schizophrenia cohort as the study cohort; the inclusion criteria for the subjects were at least one discharge diagnosis of schizophrenia (ICD-9-CM code 295.xx) and age at first psychiatric admission from 18 to 65 years ($n$ = 32 399). All of the subjects' medical records from 1 January 2000 to 31 December 2010 were retrieved. Each prescription record contained the medication, dosage, time of prescription, and duration of drug regimen.

Patients who were diagnosed with tuberculosis (ICD-9-CM codes 010.x to 018.x) before the first psychiatric admission (baseline) were excluded. All subjects were tracked from baseline until a new diagnosis of tuberculosis, death, or until 31 December 2010. The diagnosis of new tuberculosis required a record of ICD-9-CM code 010.x-018.x plus prescription of at least two antituberculosis drugs (e.g., isoniazid, ethambutol, rifampin, or pyrazinamide). Finally, 284 subjects had new diagnoses of tuberculosis and were defined as the study cases.

## Nested case–control study

We performed a nested case–control study derived from the study cohort. The date of newly diagnosed tuberculosis was defined as the index date. From the cohort, we randomly selected 10 controls or fewer without a diagnosis of tuberculosis for each case ($n$ = 284) with newly diagnosed tuberculosis, based on risk-set sampling, matched by sex, age ($\pm$5 years), and the year of first psychiatric admission. Controls were then assigned the same index date as their matched case. In addition, each control subject had at least one claim record after the index date to confirm that they were covered by the National Health Insurance program. A flow diagram of case selection is provided in Figure 1.

## Antipsychotics exposure

We retrieved data on the use of antipsychotic drugs from prescription files and calculated the durations and dosing regimens on the basis of the dispensed number of units for each patient. Second- and first-generation antipsychotics are listed in Document S1 in Appendix S1 of the supplementary material. The drugs used most commonly in Taiwan were included in the individual drug analyses.

Antipsychotic exposure in each case–control set was determined based on the following approaches. First, the temporal relationships were determined: Often after infection with *M. tuberculosis*, the immune response does not eradicate the bacteria, causing latent tuberculosis in which the bacteria assume a clinically silent, latent state of infection, from which they can be reactivated.[11] The evidence-based review study[12] recommended that patients with tuberculosis receive at least 6 months (180 days) of treatment to eradicate the bacteria. We then proposed a rationale that a specified drug exposed during the 180-day period window before the incident tuberculosis could be potentially associated with tuberculosis. Therefore, we defined the use of an antipsychotic during the 180 days before the index date as current use.

Antipsychotic use was categorized as 'previous use' if the last prescription had ended more than 180 days before the index date. 'Nonusers' were defined as the reference group in the analysis. We then estimated the temporal risk of an antipsychotic on the development of tuberculosis.

In addition, we estimated the effect of the dose dependency used in the current period on the risk of tuberculosis. The antipsychotic dose was categorized as 0, <0.5, 0.5–1.0, and >1.0 based on the average defined daily dose (DDD). The DDD was based on the dose information obtained from the Anatomical Therapeutic Chemical Classification system (ATC/DDD Index 2009; http://www.whocc.no/atc_ddd_index/ [accessed 1 May 2009]).[13] For example, 300 mg of clozapine was equivalent to one DDD. Furthermore, patients receiving clozapine treatment in Taiwan are strictly monitored for the risk of agranulocytosis and are discontinued on clozapine immediately if they present with agranulocytosis. Thus, the dataset excluded patients with clozapine-induced agranulocytosis. The risk of clozapine-induced tuberculosis was estimated based on a large-scale dataset of patients without clozapine-induced agranulocytosis.

## Potential confounders

Physical illnesses and concomitant medications prescribed within 180 days before the index date (listed in Table 1) served as covariates in the adjusted regression models, due to their potential

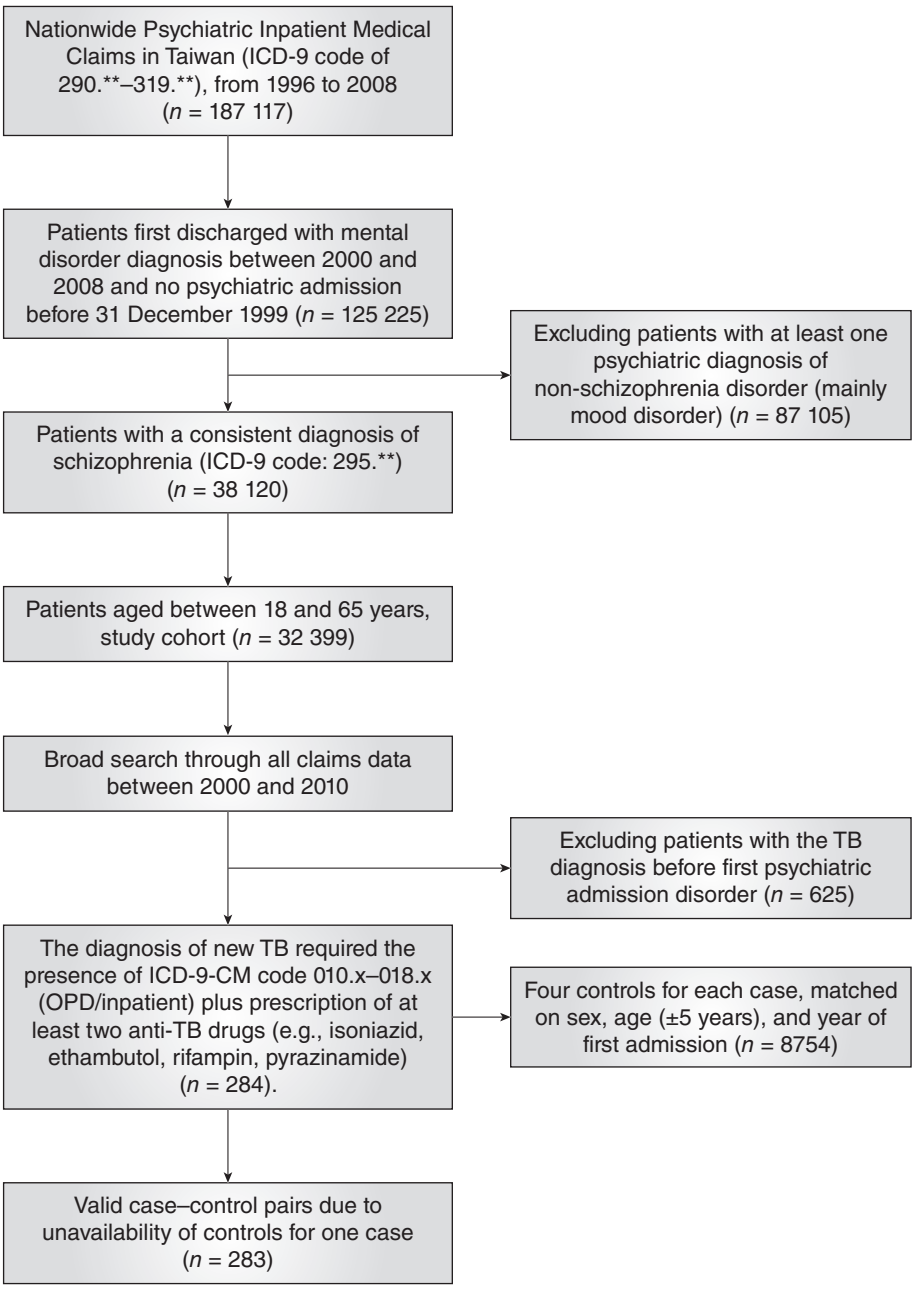


**Figure 1.** Study flow diagram. OPD, obstructive pulmonary disease.

associations with the risk of tuberculosis.[3,5,14,15] In addition, we added the Charlson Comorbidity Score[16,17] and urbanization at the first psychiatric admission as covariates in the adjusted models. The Charlson Comorbidity Score, the sum of the weighted scores of 31 comorbid conditions, is widely used to assess general health status.[16,17] We adopted urbanization stratification[18] specifically used in Taiwan, and the level of urbanization was categorized as Level 1 (highly urbanized area), Level 2 (moderately urbanized area), Level 3 (township area), and Level 4 (rural area).

## Statistical analysis

The crude incidence of newly diagnosed tuberculosis was calculated as the number of cases divided by the contributed person-years of each individual in

**Table 1.** Characteristics of case subjects with incident tuberculosis and controls derived from a nationwide cohort with schizophrenia ($n$ = 32 399)

| Characteristic $n$ (%) | Cases ($n$ = 283) | Controls ($n$ = 2820) | Risk ratio | 95% Confidence interval | $P$-value[†] |
|---|---|---|---|---|---|
| At first admission | $n$ (%) | $n$ (%) | | | |
| Men | 203 (72.5) | 2030 (72.6) | — | — | — |
| Age (years), mean (SD) | 42.7 (11.7) | 42.6 (11.6) | 1.05 | 0.76–1.44 | 0.773 |
| Charlson Comorbidity Index | | | | | |
| 1 | 230 (81.3) | 2358 (83.6) | Reference | | |
| 2 | 44 (15.6) | 393 (13.9) | 1.15 | 0.82–1.61 | 0.424 |
| ≥3 | 9 (3.2) | 68 (2.4) | 1.36 | 0.67–2.75 | 0.393 |
| Urbanization[‡] | $n$ (%) | $n$ (%) | | | |
| Level 1 | 63 (22.3) | 814 (28.9) | Reference | | |
| Level 2 | 86 (30.4) | 1117 (39.6) | 1.00 | 0.72–1.41 | 0.989 |
| Level 3 | 101 (35.7) | 692 (24.5) | 1.91 | 1.37–2.66 | <0.001 |
| Level 4 | 33 (11.7) | 197 (7.0) | 2.24 | 1.41–3.53 | <0.001 |
| Within 180 days before the index date | | | | | |
| Number of psychiatric hospital admissions, mean (SD) | 0.5 (0.8) | 0.3 (0.6) | 1.61 | 1.36–1.90 | <0.001 |
| Physical illnesses | | | | | |
| Cardiovascular disease | 97 (34.3) | 543 (19.3) | 2.39 | 1.81–3.16 | <0.001 |
| Diabetes mellitus | 42 (14.8) | 264 (9.4) | 1.72 | 1.20–2.46 | 0.003 |
| Cerebrovascular disease | 19 (6.7) | 45 (1.6) | 4.87 | 2.72–8.71 | <0.001 |
| Chronic hepatic disease | 26 (9.2) | 166 (5.9) | 1.62 | 1.05–2.49 | 0.029 |
| Cancer | 23 (8.1) | 33 (1.2) | 8.31 | 4.66–14.83 | <0.001 |
| Asthma | 15 (5.3) | 63 (2.2) | 2.46 | 1.38–4.37 | 0.002 |
| Upper respiratory tract infection | 116 (41.0) | 832 (29.5) | 1.67 | 1.30–2.15 | <0.001 |
| Delirium[§] | 2 (0.7) | 11 (0.4) | 1.82 | 0.40–8.20 | 0.437 |
| Concomitant drugs | | | | | |
| Cardiovascular drugs | | | | | |
| Antihypertensive agents | 9 (3.2) | 75 (2.7) | 1.21 | 0.60–2.44 | 0.599 |
| Beta-blocking agents | 93 (32.9) | 827 (29.3) | 1.18 | 0.91–1.54 | 0.210 |
| Calcium channel blockers | 35 (12.4) | 238 (8.4) | 1.57 | 1.06–2.31 | 0.024 |
| Agents acting on the renin-angiotensin system | 15 (5.3) | 161 (5.7) | 0.93 | 0.53–1.61 | 0.784 |
| Lipid modifying agents | 8 (2.8) | 126 (4.5) | 0.62 | 0.30–1.29 | 0.201 |
| Drugs used in diabetes | 28 (9.9) | 234 (8.3) | 1.21 | 0.80–1.84 | 0.365 |
| Antithrombotic agents | 30 (10.6) | 154 (5.5) | 2.12 | 1.39–3.25 | <0.001 |
| Corticosteroids for systemic use | 57 (20.1) | 283 (10.0) | 2.25 | 1.64–3.08 | <0.001 |
| Anti-Parkinson drugs | 192 (67.8) | 1888 (67.0) | 1.04 | 0.80–1.36 | 0.783 |
| Mood stabilizer | 70 (24.7) | 419 (14.9) | 1.90 | 1.42–2.54 | <0.001 |
| Antidepressant | 62 (21.9) | 580 (20.6) | 1.09 | 0.81–1.47 | 0.579 |

[†]Estimated using univariate conditional logistic regression.
[‡]The level of urbanization was categorized as Level 1 (highly urbanized area), Level 2 (moderately urbanized area), Level 3 (township area), and Level 4 (rural area).
[§]Based on ICD-9 code, including presenile dementia with delirium, senile dementia with delirium, arteriosclerotic dementia with delirium, alcohol withdrawal delirium, drug-induced delirium, acute delirium, and subacute delirium.

the cohort. Differences in incidence of tuberculosis among cases was investigated using Gehan's generalized Wilcoxon test[19] and life-table survival analysis.

We employed multivariate, conditional, logistic regression to estimate the risk of tuberculosis in relation to current use of individual antipsychotic

agents, the average defined daily dose of current drug use, and polypharmacy of antipsychotic agents.

The covariates used in the multivariate regression comprised all variables listed in Table 1 except the matched variables (age, sex), which included the Charlson Comorbidity Index, urbanization at the first admission, and the following variables within 180 days before the index date, including the number of psychiatric hospital admissions, physical illnesses, and concomitant medications.

Regression modelling was conducted using SAS software, version 9.2 (SAS Institutes, Inc., Cary, NC, USA). A *P*-value of 0.05 was considered significant.

### Sensitivity analysis

To assess the robustness of the results, we conducted several sensitivity analyses. First, to ensure the use of 10 controls was not inflating the statistical significance of our results, we repeated our analyses using four controls per case. Second, the assignment of antipsychotic drugs could be determined based on the presence of comorbid physical illnesses and concomitant medications due to the non-randomized study design, introducing protopathic bias.[20] We conducted a propensity score-adjusted regression to validate the associations between the specified antipsychotic agents and tuberculosis.

## RESULTS

### Incidence of newly diagnosed tuberculosis

The incidence of tuberculosis was 1.29 cases per 1000 person-years (95% confidence interval [CI]: 1.14–1.45, based on the Poisson distribution).

### Characteristics of case and control subjects

This study included 32 399 schizophrenia patients. Overall, 284 (0.88%) had newly diagnosed tuberculosis; the mean (SD) time to incidence was 3.3 (2.5) years over 10 years of follow up. We eventually matched 283 (283/284, 99.6%) patients with 2820 controls (281 cases with 10 controls, one case with six controls, one case with four controls).

Cases had similar Charlson Comorbidity Index distributions at first psychiatric admission compared to controls (Table 1), but patient cases had a higher level of urbanization. In addition, cases had greater numbers of physical illnesses and used greater numbers of concomitant drugs than did controls.

### Effects of antipsychotic agents on the temporal risk of tuberculosis

Table 2 shows that current use of any second-generation antipsychotic was not associated with risk of tuberculosis; neither was current use of any first-generation antipsychotics. As for the individual antipsychotics studied, clozapine was the only antipsychotic agent with a significantly elevated risk of tuberculosis (adjusted risk ratio = 1.63, $P = 0.014$) based on the temporal relationship. Current use of non-clozapine antipsychotics was not associated with risk of tuberculosis.

Furthermore, we plotted the survival curves for the cumulative incidence of tuberculosis between clozapine and non-clozapine users (Fig. 2), respectively. The clozapine users were the patients who received clozapine treatment within 180 days before the censor (i.e., the incident tuberculosis), mortality, or the end of the study (31 December 2012). The incidence differed significantly between the two groups ($P = 0.006$, by life-tables analysis).

### Clozapine dose dependency and tuberculosis

By stratifying the clozapine daily dose (Table 3), we found that patients taking low average DDD (0.1–0.5) had a higher risk of tuberculosis (adjusted risk ratio = 2.15, $P = 0.046$), than those taking high average DDD (>1.0; adjusted relative risk [RR] = 1.70, $P = 0.030$). However, those taking mid-level average DDD of clozapine were not associated with the risk of tuberculosis. The above findings show no obvious dose-dependency relationships. Other individual antipsychotics showed no significant associations for DDD.

### Effect of clozapine combination therapy on the risk of tuberculosis

A substantial portion of patients and control subjects had current use of clozapine in combination with other antipsychotic agents. Relative to single use of clozapine, Table 4 shows that patients with schizophrenia had a significantly high risk of tuberculosis when clozapine was combined with another antipsychotic agent (adjusted RR = 2.30, $P = 0.044$). No other individual antipsychotics showed any significant associations in the analyses of combination treatment sets.

**Table 2.** Association between tuberculosis and the use of antipsychotic drugs in case subjects and controls stratified by current use, previous use, and no use (reference stratum)

| | Cases ($n$ = 283) $n$ (%) | Controls ($n$ = 2820) $n$ (%) | Adjusted risk ratio† | Model 95%CI | $P$-value | | Cases ($n$ = 283) $n$ (%) | Controls ($n$ = 2820) $n$ (%) | Adjusted risk ratio† | Model 95%CI | $P$-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Any use of second-generation antipsychotics | | | | | | Any use of first-generation antipsychotics | | | | | |
| No use | 71 (25.1) | 734 (26.0) | Reference | — | | No use | 7 (2.5) | 71 (2.5) | Reference | — | |
| Previous use | 56 (19.8) | 576 (20.4) | 0.99 | 0.66–1.48 | 0.959 | Previous use | 103 (36.4) | 1264 (44.8) | 0.74 | 0.32–1.72 | 0.487 |
| Current use | 156 (55.1) | 1510 (53.6) | 0.92 | 0.66–1.29 | 0.630 | Current use | 173 (61.1) | 1485 (52.7) | 0.97 | 0.42–2.23 | 0.935 |
| Clozapine | | | | | | Chlorpromazine | | | | | |
| No use | 223 (78.8) | 2354 (83.5) | Reference | — | | No use | 186 (65.7) | 1969 (69.8) | Reference | — | |
| Previous use | 18 (6.4) | 193 (6.8) | 0.92 | 0.54–1.57 | 0.748 | Previous use | 72 (25.4) | 679 (24.1) | 0.94 | 0.68–1.30 | 0.708 |
| Current use | 42 (14.8) | 273 (9.7) | 1.63* | 1.10–2.40 | 0.014 | Current use | 25 (8.8) | 172 (6.1) | 1.25 | 0.76–2.05 | 0.387 |
| Olanzapine | | | | | | Haloperidol | | | | | |
| No use | 206 (72.8) | 2117 (75.1) | Reference | — | | No use | 50 (17.7) | 547 (19.4) | Reference | — | |
| Previous use | 52 (18.4) | 414 (14.7) | 1.30 | 0.91–1.87 | 0.150 | Previous use | 143 (50.5) | 1580 (56.0) | 1.00 | 0.70–1.45 | 0.988 |
| Current use | 25 (8.8) | 289 (10.3) | 0.78 | 0.49–1.25 | 0.305 | Current use | 90 (31.8) | 693 (24.6) | 1.14 | 0.76–1.73 | 0.528 |
| Quetiapine | | | | | | Flupentixol | | | | | |
| No use | 212 (74.9) | 2257 (80.0) | Reference | — | | No use | 193 (68.2) | 2069 (73.4) | Reference | — | |
| Previous use | 43 (15.2) | 359 (12.7) | 1.34 | 0.91–1.96 | 0.139 | Previous use | 65 (23.0) | 538 (19.1) | 1.19 | 0.86–1.64 | 0.300 |
| Current use | 28 (9.9) | 204 (7.2) | 1.12 | 0.70–1.81 | 0.628 | Current use | 25 (8.8) | 213 (7.6) | 1.13 | 0.70–1.84 | 0.615 |
| Zotepine | | | | | | Sulpiride | | | | | |
| No use | 217 (76.7) | 2277 (80.7) | Reference | — | | No use | 72 (25.4) | 725 (25.7) | Reference | — | |
| Previous use | 42 (14.8) | 365 (12.9) | 1.13 | 0.76–1.68 | 0.538 | Previous use | 136 (48.1) | 1447 (51.3) | 0.77 | 0.55–1.07 | 0.120 |
| Current use | 24 (8.5) | 178 (6.3) | 1.30 | 0.78–2.16 | 0.310 | Current use | 75 (26.5) | 648 (23.0) | 0.96 | 0.65–1.40 | 0.815 |
| Risperidone | | | | | | | | | | | |
| No use | 133 (47.0) | 1260 (44.7) | Reference | — | | | | | | | |
| Previous use | 72 (25.4) | 852 (30.2) | 0.76 | 0.55–1.06 | 0.109 | | | | | | |
| Current use | 78 (27.6) | 708 (25.1) | 0.87 | 0.63–1.22 | 0.423 | | | | | | |
| Amisulpride | | | | | | | | | | | |
| No use | 256 (90.5) | 2600 (92.2) | Reference | — | | | | | | | |
| Previous use | 19 (6.7) | 115 (4.1) | 1.52 | 0.86–2.69 | 0.153 | | | | | | |
| Current use | 8 (2.8) | 105 (3.7) | 0.66 | 0.30–1.44 | 0.298 | | | | | | |
| Aripiprazole | | | | | | | | | | | |
| No use | 273 (96.5) | 2705 (95.9) | Reference | — | | | | | | | |
| Previous use | 9 (3.2) | 62 (2.2) | 1.66 | 0.75–3.66 | 0.209 | | | | | | |
| Current use | 1 (0.4) | 53 (1.9) | 0.15 | 0.02–1.13 | 0.065 | | | | | | |

*$P < 0.05$.
†Adjusted for Charlson Comorbidity Index, urbanization at the first admission, and the following variables within 180 days before the index date, including the number of psychiatric hospital admissions, physical illnesses, and concomitant medications (listed in Table 1).

### Sensitivity analysis

In the sensitivity analysis, the results were almost identical using four controls per case (current clozapine use: adjusted risk ratio, 1.60; 95%CI, 1.03–2.47; $P$ = 0.035) compared to 10 controls; thus 10 controls were used.

Second, results were similar in the propensity-score adjusted analyses and showed the robustness of the findings. For instance, compared with patients who did not use clozapine currently, the adjusted RR for current users were 1.63 (95%CI: 1.10–2.40, $P$ = 0.014) in the multivariate adjusted model and 1.64 (95%CI: 1.11–2.42, $P$ = 0.014) in the propensity score-adjusted model (Table S1 in Appendix S1).

## DISCUSSION

### Main findings

We investigated the association between antipsychotics and tuberculosis using a large-scale population dataset. In this nationwide, case–control study of schizophrenic patients, only clozapine use was associated with a risk of tuberculosis. In addition, the association did not show clear dose-dependency, and clozapine combined with other antipsychotics

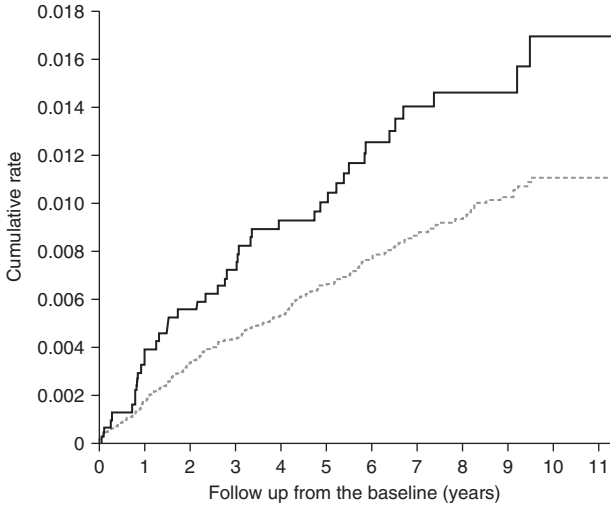


**Figure 2.** Cumulative incidence of tuberculosis in the cohort with schizophrenia stratified by the use or non-use of clozapine within 180 days before the censor (i.e., the incident tuberculosis, mortality, or the end of the study). (——) Clozapine users. (- - - - -) Non-clozapine users.

showed a synergistic risk of tuberculosis. Besides, we found that living in a less urbanized area, many psychiatric hospital admissions, and several comorbid physical illnesses and their related concomitant medications were associated with the risk of tuberculosis.

## Factors associated with tuberculosis

The incidence of tuberculosis was 1.29 cases per 1000 person-years, which was higher than the incidence of tuberculosis in the general population in Taiwan in 2010 (0.57 per 1000 person-years).[21] The finding was in line with a prior study,[4] revealing that schizophrenia patients were the high-risk group for tuberculosis. Prior studies showed that, in the general population, several medical comorbidities were associated with greater risks of tuberculosis, including diabetes mellitus,[22] malignant disease,[22] alcohol use,[23] HIV infection,[24] and chronic obstructive pulmonary disease.[25] Similarly, in our schizophrenic cohort, diabetes mellitus, malignant diseases, and chronic obstructive pulmonary disease were also associated with higher risks of tuberculosis.[22] Despite prior studies showing that HIV was associated with tuberculosis,[24] we found no similar situation. We observed that the prevalence of HIV infection in our schizophrenia patients was too small to detect any meaningful association. A prior study in Taiwan similarly reported a low prevalence of HIV in psychiatric patients.[26]

Regarding urbanization, most studies showed that the risk of tuberculosis was higher among populations living in urbanized areas.[27,28] In contrast, our findings showed that less urbanization produced a greater risk of tuberculosis. On the contrary, it is in the rural areas of Taiwan that inhabitants' socioeconomic status is disadvantaged by hygienic conditions and the availability and access to health services compared to the inhabitants of urbanized areas.

## Effect of clozapine on the risk of tuberculosis

Clozapine was the only antipsychotic agent associated with an increased risk of tuberculosis. After

**Table 3.** Association between tuberculosis and the dose (average defined daily dose) of current use (within 180 days before the index date) of individual antipsychotic drugs in case subjects and controls

| | Cases ($n$ = 283) $n$ (%) | Controls ($n$ = 2820) $n$ (%) | Unadjusted risk ratio | Model 95%CI | $P$-value | Adjusted risk ratio† | Model† 95%CI | $P$-value |
|---|---|---|---|---|---|---|---|---|
| Average defined daily dose | | | | | | | | |
| Clozapine | | | | | | | | |
| <0.1 | 242 (85.5) | 2569 (91.1) | Reference | — | | Reference | — | |
| 0.1–0.5 | 10 (3.5) | 44 (1.6) | 2.42* | 1.20–4.87 | 0.013 | 2.15* | 1.01–4.58 | 0.046 |
| 0.5–1.0 | 6 (2.1) | 38 (1.4) | 1.73 | 0.72–4.17 | 0.222 | 1.21 | 0.45–3.27 | 0.713 |
| >1.0 | 25 (8.8) | 169 (6.0) | 1.57* | 1.01–2.44 | 0.046 | 1.70* | 1.05–2.74 | 0.030 |

*$P$ < 0.05.
†Adjusted for Charlson Comorbidity Index, urbanization at the first admission, and the following variables within 180 days before the index date, including the number of psychiatric hospital admissions, physical illnesses, and concomitant medications (listed in Table 1).

**Table 4.** Association between tuberculosis and the current use of clozapine, which was stratified into three strata: Single clozapine use (reference stratum), combined use with other antipsychotics, and no current use

| | Cases ($n$ = 283) $n$ (%) | Controls ($n$ = 2820) $n$ (%) | Unadjusted Risk ratio | Model 95%CI | Adjusted Risk ratio[†] | Model 95%CI |
|---|---|---|---|---|---|---|
| Clozapine | | | | | | |
| Only clozapine | 21 (7.4) | 190 (6.7) | Reference | — | Reference | — |
| Combined with other antipsychotic drugs | 15 (5.3) | 59 (2.1) | 2.33* | 1.12–4.84 | 2.30* | 1.02–5.17 |
| No current use | 247 (87.3) | 2571 (91.2) | 0.87 | 0.54–1.39 | 0.83 | 0.50–1.39 |

*$P < 0.05$

[†]Adjusted for Charlson Comorbidity Index, urbanization at the first admission, and the following variables within 180 days before the index date, including the number of psychiatric hospital admissions, physical illnesses, and concomitant medications (listed in Table 1).

adjustment for possible confounders, clozapine use was associated with a 63% increased risk of tuberculosis. Few, if any, studies have explored the risk of clozapine on tuberculosis. Although the risk mechanism remains speculative, studies on other clozapine side-effects, such as agranulocytosis and pneumonia, could help shed light on this issue. Clozapine-induced agranulocytosis is a well-known, serious adverse effect and its etiologic mechanism is unknown. Several hypotheses have been proposed, including an immune process and induction of neutrophil apoptosis, although neither has been proven as the pathophysiology behind agranulocytosis.[29,30] As a side-effect of agranulocytosis, tuberculosis is related to immune dysfunction as well.

As mentioned in the Methods, schizophrenia patients with clozapine-induced agranulocytosis were excluded from the dataset. This study estimated the risk of clozapine-induced tuberculosis among a schizophrenia cohort without clozapine-induced agranulocytosis. The mechanism for a weakened immune reaction resulting in the development of tuberculosis could be different from that of agranulocytosis.

As for the infection with *M. tuberculosis*, the process of reactivation of latent tuberculosis is obscure; however, immunological factors play an important role in this process. Data from human diseases and experimental animal models suggest CD4+ T cells, interleukin-12, interferon-γ, and tumor necrosis factor-α help control *M. tuberculosis* infection.[11,31] We propose that clozapine modulates immune function and possibly promotes tuberculosis reactivation from latent disease.

The risk of pneumonia is highest with clozapine in comparison with other antipsychotics,[3] which is consistent with the results of this study. This study showed clear evidence that clozapine was associated with tuberculosis, but not other antipsychotics. Compared with other antipsychotics, clozapine has high affinities for histaminergic-1 and muscarinic-1 receptors, which likely account for its prominent association with pneumonia.[3] Like pneumonia, tuberculosis is an infection that takes a chronic protracted course and requires a long period of treatment. The histaminergic-1 and muscarinic-1 receptors could be associated with toxic effects on the immune system, thus weakening the immune system. Additionally, studies suggest that clozapine causes immunotoxicity at the cellular level by decreasing spleen cellularity, and circulating neutrophils and lymphocytes.[32,33] In the future, further large-scale human and animal studies are warranted to prove these assumptions.

## Effect of dose-dependency on risk of tuberculosis

Prior studies demonstrated that some side-effects of clozapine, such as seizures, were dose-dependent,[34] but agranulocytosis was not.[34–36] Intriguingly, similar to agranulocytosis, we found that the effect of clozapine on the risk of tuberculosis was not dose-dependent. Both tuberculosis and agranulocytosis are highly related to immune system function. Further study is required to determine why clozapine weakens the immune system, but not in a dose-dependent manner.

### Effect of clozapine combination therapy on risk of tuberculosis

Clozapine combined with other antipsychotic agents has a synergistic effect on the risk of numerous side-effects, including blood dyscrasias,[29,37] diabetes mellitus,[38] and pneumonia.[3] Studies showed that clozapine recipients experienced more adverse drug reactions related to decreases in white blood cells or absolute neutrophil counts while using concomitant medications, including autonomic agents, anti-infective agents, and gastrointestinal agents.[29,37] Patients receiving clozapine combined with other antipsychotics had a higher risk of diabetes mellitus than patients not taking combination treatment.[38] Additionally, clozapine combined with other antipsychotics resulted in a greater synergistic risk of pneumonia than clozapine monotherapy.[3] Similar to these studies, we found that clozapine combined with other antipsychotic agents was associated with a significant risk of tuberculosis. Although clinical guidelines suggest that a second antipsychotic in addition to clozapine could improve functioning and decrease symptoms in partially responsive patients with schizophrenia,[39] we recommend that clinicians prescribe combination therapy (clozapine plus another antipsychotic drug) cautiously, and monitor such patients with periodic chest X-rays.

### Limitations

Certain limitations should be considered when interpreting the results. First, according to the case definition, patients with tuberculosis did not include those with latent tuberculosis (ICD 9 code 795.5 nonspecific reaction to the tuberculin test). Thus, we could not determine the risk of clozapine associated with latent tuberculosis. Nonetheless, clozapine could affect the risk of transformation of latent to activated tuberculosis. Future studies are needed.

Second, even though we controlled for physical illnesses and concomitant medications in the risk estimation of clozapine on tuberculosis, the risk could be confounded by unmeasured covariates, such as malnutrition. We were unable to obtain information on malnutrition from the dataset; thus, we used urbanization as a surrogate for the adjustment.

Third, we could not assess adherence to the medications because these data were unavailable in the claims database. Nevertheless, nonadherence would result in nondifferentiated misclassification of antipsychotic exposure, which would most likely lead to underestimation of the actual risk.

Fourth, the number of incident tuberculosis cases in this study was limited, especially the number in each category of the used dose of clozapine. For example, among the incident tuberculosis cases ($n$ = 283) and the matched controls ($n$ = 2820), only six (2.1%) and 38 (1.4%) used the moderate dose of clozapine (0.5–1.0 DDD per day) in the current use period, respectively. This could explain why this study did not show a dose-dependent relation between the use of clozapine and tuberculosis. The dose-dependent relation needs to be validated by a future large-scale study.

### Implications

Schizophrenic patients are particularly prone to tuberculosis if they have medical comorbidities and take immune-modulating medications. The exploratory findings show evidence for an association between clozapine and the risk of tuberculosis, but not in a clearly dose-dependent manner. The use of clozapine with other antipsychotic agents could have a synergistic effect on the risk of tuberculosis compared to clozapine monotherapy. This exploratory study suggests the potential effect of clozapine on the risk of tuberculosis, especially for those on clozapine in combination with other antipsychotics. Replication studies for confirmation are required.

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## DISCLOSURE STATEMENT

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## AUTHOR CONTRIBUTIONS

H.-C.L., G.C.-L.H., and C.-J.K. conceived and designed the study. S.-Y.Y. acquired the data. Y.T.L. performed the statistical analysis. C.-H.P. and C.C.C. provided administrative and material support. H.-C. L. and C.-J.K. drafted the manuscript. H.-C.L. made critical revisions to the manuscript for important intellectual content, and C.-J.K. supervised the study.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Appendix S1.** List of Supporting Information.
**Table S1.** Risk of individual second-generation antipsychotic drugs on the incidence of tuberculosis estimated by means of adjusted model and propensity score-adjusted model separately
**Doc S1.** List of first- and second-generation antipsychotics included in this study