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Case–Control Study Investigating the Association Between Use of Selective Serotonin Reuptake Inhibitors and Pulmonary Tuberculosis in Taiwan

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Abstract

Background and Objective: The aim of the study was to investigate whether use of selective serotonin reuptake inhibitors (SSRIs) was associated with pulmonary tuberculosis.

Methods: The case–control study was conducted to analyze the database between 2000 and 2013. Patients aged 20 to 84 years with newly diagnosed pulmonary tuberculosis were selected as the cases (n = 8593). Participants without pulmonary tuberculosis were selected as the controls (n = 43 472). Patients who never had a prescription for SSRIs were defined as never use. Those who ever had a prescription for SSRIs were defined as ever use.

Results: The adjusted odds ratio (OR) of pulmonary tuberculosis was 1.03 for patients with ever use of SSRIs (95% confidence interval [CI]: 0.93-1.14), compared to never use. The adjusted OR of pulmonary tuberculosis was 1.00 for patients with increasing cumulative duration of SSRI use for every 1 month (95% CI: 0.99-1.00), compared to never use. The adjusted OR of pulmonary tuberculosis was 0.99 for patients with increasing cumulative dosage of SSRI use for every 1 mg (95% CI: 0.99-1.00), compared to never use.

Conclusion: No significant association can be detected between SSRI use and pulmonary tuberculosis in Taiwan. No duration-dependent effect or dose-dependent effect of SSRIs use can be detected on the risk of pulmonary tuberculosis.

Keywords

selective serotonin reuptake inhibitors, pulmonary tuberculosis, case–control study, national health insurance program, Taiwan

Introduction

Tuberculosis (TB) is a major public health issue with a relatively high incidence and prevalence which has burdened all aspects, including psychological social and biology. It is also a chronic infectious multisystemic disease in the past few decades. According to the World Health Organization (WHO) report, at least 10.4 million people demonstrated new incidents of TB worldwide in 2014.[1] Most global new cases of TB occurred in some developing Asian countries, such as Bangladesh, China, India, and Pakistan from WHO data.[2] In addition to developing countries, 4% to 6% of the population in the United States have latent infections of TB.[3] From previous study in Taiwan, the annual incidence was 63.7 cases per 100 000 person-years in 2006.[4] By efforts of Taiwan Centers for Disease Control, we paid attention to declining trend of TB

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over the past years.[5] After all control measurements, including directly observed treatment, short course (DOTS) for sputum smear-positive patients, and DOTS-plus strategy for patients with multidrug resistance TB, the death rate was down to 2.8 per 100 000 populations.[6] Otherwise, until 2009, the success rate for treating TB is up to 87% in Taiwan.[7]

Serotonin (5-hydroxytryptamine, 5-HT), is a monoamine neurotransmitter which is biochemically derived from amino acid tryptophan, mainly detected in the gastrointestinal tract and central nervous system in human beings.[8] It is also well known for contributing to the etiology of happiness and well-being experienced by human beings.[9] Otherwise, serotonin is metabolized by monoamine oxidase to the corresponding aldehyde, which is mainly carried on in the liver. Monoamine oxidase inhibitors prevent the catabolism of most neurotransmitters, including serotonin, thereby increasing the plasma levels in the brain which resulted in happiness and euphoria.[10] Due to the former mechanism, drugs that can alter serotonin levels in plasma are used for treating major depressive disease.

According to previous published worldwide research, 20% of patients with somatic disease have major depression.[11] The lifetime prevalence of mood disorder in patients with chronic disease is 8.9% to 12.9%, with a 6-month prevalence of 5.8% to 9.4%.[12] On the contrary, patients with pulmonary disease, in particular chronic disease, including bronchial asthma, chronic obstructive pulmonary disease, and TB hospitalized patients, were severely impaired due to chronic psychogenic condition.[13] At the same time, some literature revealed that depression was associated with chronic pulmonary disease, especially TB.[11,14] Furthermore, from published article in 2017, depression is associated with 1.15-fold increased hazard of pulmonary TB in Taiwan.[15] Base on the already existing mutual relationship between depression and pulmonary TB from previous articles, we hypothesized making a link between depression and pulmonary TB because of lower immunity. Owing to the reasons mentioned subsequently, (1) no study exists that explores the relationship between selective serotonin reuptake inhibitors (SSRIs) and TB in Taiwan and also worldwide; (2) SSRIs are commonly used globally, and any potential risk of increasing disease incidence due to its side effects have important clinical implications; and (3) previous localized article associated with depression and TB were scarce and just focused on disease instead of treatment. We used large-scale National Health Insurance (NHI) data to investigate the relationship between SSRI use and TB.

Methods

Study Design and Data Source

Taiwan is an independent country with more than 23 million persons.[16-18] A case–control study was conducted to analyze the database of the Taiwan National Health Insurance Program. The program was launched in March 1995, and now it has covered around 99.6% of persons living in Taiwan.[19] The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115). The details of the program have been written in previous studies.

Selection of Cases and Controls

We selected patients aged 20 to 84 years with newly diagnosed pulmonary TB (*The International Classification of Diseases, Ninth Edition* [*ICD-9*] codes 010, 011, 012, and 018) between 2000 and 2013 as the cases with pulmonary TB. The index date was defined as the date of the cases being diagnosed with pulmonary TB. We randomly selected patients without pulmonary TB aged 20 to 84 years from the same database as the controls. Both cases and controls were matched with sex, age (every 5-year interval), and the year of index date.

Potential Confounders

Medical conditions that could be related to pulmonary TB were included as follows: alcohol-related disease, cancer, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, and chronic liver disease including cirrhosis, hepatitis B, hepatitis C, and other chronic hepatitis. All comorbidities were diagnosed based on *ICD-9* codes. The accuracy of *ICD-9* codes has been validated in previous studies.[20-23]

Definition of SSRI Use and Corticosteroid Use

The prescription histories of medications studied were collected in the study. The definition of medication use was adapted from previous studies.[24-26] Ever use of medication was defined as a patient who had at least a prescription of medications before the index date. Never use of medication was defined as a patient who never had a prescription of medications before the index date.

Statistical Analysis

Distributions of sex, age, SSRI use, corticosteroids use, and comorbidities between the cases and controls were compared by the χ^2 test for categorized variables and the t test for continuous variables. Initially, all variables were included in the univariable logistic regression model. Variables found to be statistically significant in the univariable model were further examined in the multivariable logistic regression model. We measured the odds ratio (OR) and the 95% confidence interval (CI) for pulmonary TB associated with SSRI use. We further conducted an analysis to investigate whether there were duration-dependent and dose-dependent effects of SSRIs on the risk of pulmonary TB. All data processing and statistical analyses were performed with the SAS software version 9.2 (SAS Institute, Inc, Cary, North Carolina). A 2-tailed P value $<.05$ was considered statistically significant.

Table 1. Characteristics and Comorbidities Between Cases With Pulmonary Tuberculosis and Controls.[a]

Variable	Controls, n = 43 472 n (%)	Cases, n = 8593 n (%)	*P* Value[b]
Sex			.99
Female	10 728 (31.2)	2682 (31.2)	
Male	23 644 (68.8)	5911 (68.8)	
Age-group, years			.99
20-39	10 396 (30.3)	2599 (30.3)	
40-64	8504 (24.7)	2126 (24.7)	
65-84	15 472 (45.0)	3868 (45.0)	
Age, years, mean ± standard deviation[c]	58.8 ± 17.2	59.0 ± 17.1	.59
Ever use of selective serotonin reuptake inhibitors	1810 (5.27)	619 (7.20)	<.001
Ever use of corticosteroids	28 186 (82.0)	7584 (88.3)	<.001
Comorbidities before index date			
Alcohol-related disease	1174 (3.42)	754 (8.77)	<.001
Cancer	1238 (3.60)	489 (5.69)	<.001
Chronic kidney disease	1942 (5.65)	713 (8.30)	<.001
Chronic liver disease	4437 (12.9)	1619 (18.4)	<.001
Chronic obstructive pulmonary disease	5207 (15.2)	3259 (37.9)	<.001
Diabetes mellitus	2807 (8.17)	1373 (16.0)	<.001

[a]Data are presented as the number of patients in each group with percentages given in parentheses.
[b]Chi-square test.
[c]*t* test comparing cases with pulmonary tuberculosis and controls.

Results

Characteristics of the Study Population

Table 1 reveals the distributions of sex, age, SSRI use, corticosteroid use, and comorbidities between the cases and controls. The study included 8593 cases with pulmonary TB and 43 472 controls, with similar distributions of sex and age. The mean ages (standard deviation) of the study patients were 59.0 (17.1) years for the cases and 58.8 (17.2) years for the controls, without statistical significance (*t* test, $P = .59$). The cases had a statistically higher proportion of ever use of SSRIs than the controls (7.20% vs 5.27%, χ^2 test, $P < .001$). The cases had statistically higher proportions of ever use of corticosteroids, alcohol-related disease, cancer, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and diabetes mellitus than the controls (χ^2 test, $P < .001$).

Association of Pulmonary TB With Use of SSRIs

Variables found to be statistically significant in the univariable logistical regression model were further included in the multivariable logistical regression model. After adjustment for confounders, the multivariable logistic regression model revealed that the adjusted OR of pulmonary TB was 1.03 for patients with ever use of SSRIs (95% CI: 0.93-1.14), compared to never use. In addition, corticosteroids use, alcohol-related disease, cancer, chronic liver disease, chronic obstructive pulmonary disease, and diabetes mellitus were associated with pulmonary TB (Table 2).

Association of Pulmonary TB With Cumulative Duration of SSRI Use

We conducted an analysis for the duration-dependent effect of SSRI use on the risk of pulmonary TB (Table 3). After adjustment for confounders, the adjusted OR of pulmonary TB was 1.00 for patients with increasing cumulative duration of SSRI use for every 1 month (95% CI: 0.99-1.00), compared to never use. There was no duration-dependent effect of SSRIs use on the risk of pulmonary TB.

Association of Pulmonary TB With Cumulative Dosage of SSRI Use

We conducted an analysis for the dose-dependent effect of SSRIs on the risk of pulmonary TB (Table 4). After adjustment for confounders, the adjusted OR of pulmonary TB was 0.99 for patients with increasing cumulative dosage of SSRIs use for every 1 mg (95% CI: 0.99-1.00), compared to never use. There was no dose-dependent effect of SSRI use on the risk of pulmonary TB.

Discussion

In this case–control study, we did not find a significant association between pulmonary TB risk and SSRI use (Table 2), a duration-dependent effect between pulmonary TB risk and SSRI use (Table 3), and a dose-dependent effect between pulmonary TB risk and SSRI use (Table 4). The adjusted OR lost the significance compared to crude OR, we tried to explained and listed reasons mentioned below. First of all, other confounding factors were considered. We also noted that corticosteroid use, alcohol-related disease, cancer, chronic liver disease, chronic obstructive pulmonary disease, and diabetes mellitus were related to pulmonary TB; the results from our study were consistent with previous studies.[27-29] Second, adjusted OR was multivariable logistical regression model, compared to crude OR which was univariable logistical regression model. Third, SSRIs were also used for the treatment of another disease except depression in clinical practice, and fewer people with depressive disorders were treated with SSRIs in the TB group (410 cases, 4.77%) and in the non-TB group (1237 cases, 2.84%). Maybe most researchers enrolled in our study were not cases with depression, thus resulting in this phenomenon.

To the best of our knowledge, this is the first case–control study to explore the relationship between pulmonary TB and SSRIs worldwide. Although the results revealed no association between pulmonary TB and SSRIs, its clinical implications were important, which provided the local physicians and psychiatrists more information about pulmonary TB and relative drug use. We could hypothesize temporarily that SSRI use is not associated with pulmonary TB risk, but not all antidepressants drugs have the same result with SSRIs for developing

Table 2. OR and 95% CI of Pulmonary Tuberculosis Associated With Use of Selective Serotonin Reuptake Inhibitors and Corticosteroids, and Comorbidities by Logistical Regression Mode.

	Crude		Adjusted [a]	
Variable	OR	95% CI	OR	95% CI
Sex (male vs female)	1.00	0.95-1.05		
Age (per 1 year)	1.00	0.99-1.00		
Ever use of selective serotonin reuptake inhibitors (never use as a reference)	1.40	1.27-1.54	1.03	0.93-1.14
Ever use of corticosteroids (never use as a reference)	1.65	1.54-1.77	1.22	1.13-1.32
Comorbidities before index date (yes vs no)				
Alcohol-related disease	2.72	2.47-2.99	2.42	2.18-2.67
Cancer	1.62	1.45, 1.80	1.32	1.18-1.48
Chronic kidney disease	1.51	1.38-1.65	1.04	0.94-1.14
Chronic liver disease	1.57	1.47-1.67	1.13	1.06-1.21
Chronic obstructive pulmonary disease	3.42	3.25-3.61	3.16	2.99-3.34
Diabetes mellitus	2.14	2.00-2.29	1.82	1.70-1.96

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Variables found to be statistically significant in the univariable logistical regression model were further included in the multivariable logistical regression model. Adjusted for corticosteroids use, alcohol-related disease, cancer, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and diabetes mellitus.

Table 3. OR and 95% CI of Pulmonary Tuberculosis Associated With Cumulative Duration of Use of Selective Serotonin Reuptake Inhibitors by Logistical Regression Model.

Variable	Case Number/ Control Number	Crude OR	95% CI	Adjusted OR[a]	95% CI
Never use of selective serotonin reuptake inhibitors as a reference	7974/32 562	1.00	Reference	1.00	Reference
Cumulative duration of selective serotonin reuptake inhibitor use (increase in duration for every 1 month)	619/1810	0.99	0.99-1.00	1.00	0.99-1.00

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Variables found to be statistically significant in the univariable logistical regression model were further included in the multivariable logistical regression model. Adjusted for corticosteroids use, alcohol-related disease, cancer, chronic kidney disease, chronic liver, chronic obstructive pulmonary disease, and diabetes mellitus.

Table 4. OR and 95% CI of Pulmonary Tuberculosis Associated with Cumulative Dosage of Selective Serotonin Reuptake Inhibitors by Logistical Regression Model.

Variable	Case Number/ Control Number	Crude OR	95% CI	Adjusted OR[a]	95% CI
Never use of selective serotonin reuptake inhibitors as a reference	7974/32 562	1.00	Reference	1.00	Reference
Cumulative dosage of selective serotonin reuptake inhibitor use (increase in dosage for every 1 mg)	619/1810	1.00	0.99-1.00	0.99	0.99-1.00

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Variables found to be statistically significant in the univariable logistical regression model were further included in the multivariable logistical regression model. Adjusted for corticosteroids use, alcohol-related disease, cancer, chronic kidney disease, chronic liver, chronic obstructive pulmonary disease, and diabetes mellitus.

pulmonary TB. Moreover, an ideal research is needed to examine the risk of pulmonary TB and another kind of antidepressants use in Taiwan and even spread to worldwide in the future.

Limitation

Some limitations need to be further discussed. First, owing to the inherent limitation of only the database use (eg, not all kinds of depression medication were enrolled due to more side effect or lower usage rate), we could not ensure the compliance of enrolled patients for following the depression or pulmonary TB treatment plan. The NHI database enables only 6 diagnoses for each case and physician's individual opinions or recall bias; coding of diagnosis might be a mistake if patient has more than 6 underlying diseases. Second, more accurate tools for the diagnosis of pulmonary TB, such as chest radiographic films or sputum culture, are necessary. Therefore, the actual number of pulmonary TB in depression populations under SSRI

medication may be underestimated or overestimated. Third, as the diagnosis of pulmonary TB requires long-term observation for its clinical manifestation, the shorter observation period in our study may have been insufficient to estimate the pulmonary TB risk compared to general populations in clinics or hospitals.

Strength

One of the primary and major strength of this study is that our article is a unique, novel, and first case–control study in the world to explore the relationship between pulmonary TB and SSRIs. Otherwise, we also enrolled large populations with study conducting better statistical power and design from the Taiwan National Health Insurance Program in the past years in Taiwan. Finally, and the most important, we focused not only on dose but also on duration level of SSRIs in the risk of pulmonary TB.

Conclusion

No significant association can be detected between SSRI use and the risk of pulmonary TB in Taiwan. No duration-dependent effect or dose-dependent effect can be detected on the risk of pulmonary TB. Further clinical research and trials are needed to explore and confirm our study findings. Close collaboration among clinical physicians, research scientists, and public health workers is indeed necessary for exploring the complex relationship between pulmonary TB, comorbidities, and SSRI use in the future.

Authors' Note

Insurance reimbursement claims data used in this study were available for public access. Patient identification numbers had been scrambled to ensure confidentiality. Patient informed consent was not required. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115). Kao-Chi Cheng and Kuan-Fu Liao participated in the data interpretation, revised the article, and contributed equally to the article. Cheng-Li Lin conducted the data analysis and revised the article. Shih-Wei Lai contributed to the conception of the article, initiated the draft of the article, and revised the article.

Declaration of Conflicting Interests

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