Typical Antipsychotics Increase Risk of Severe Exacerbation in Asthma Patients– A Nationwide Population-Based Cohort Study

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Abstract

Background:

Severe asthma exacerbation reduces patients' life quality, results in visits to the emergency department (ED) and hospitalization, and incurs additional medical costs. Antipsychotics block receptors with bronchodilation function; however, the effects of antipsychotics use on severe asthma exacerbation are unknown. This study aimed to investigate the effects of antipsychotics on asthma-related ED visits and hospitalizations.

Methods:

This study used a case-crossover design. Using the 2003-2017 Taiwan National Health Insurance Reimbursement Database, we established a cohort of 18,657 adults with severe asthma exacerbation leading to ED visits or hospitalization. Univariate and multivariate conditional logistic regressions were conducted to explore the association of antipsychotics use with severe asthma exacerbation. Subgroup analyses of different classes, doses, receptor functions of antipsychotics and schizophrenia were also performed.

Results:

Antipsychotics use was associated with a higher risk of severe asthma exacerbation (adjusted odds ratio (OR): 1.27; 95% confidence interval (CI): 1.05-1.54; $P = 0.013$) compared with no use of antipsychotics. Use of typical antipsychotics increased the risk of severe asthma exacerbation (adjusted OR: 1.40, 95% CI: 1.10-1.79, $P = 0.007$), whereas use of atypical antipsychotics did not. There was a dose-dependent effect of antipsychotics (test for trend: $P = 0.025$). Antipsychotics that block the M2 muscarinic or D2 dopaminergic receptor were associated with an increased risk of severe asthma exacerbation (adjusted OR: 1.39, 95% CI: 1.10-1.76, $P = 0.007$ and adjusted OR: 1.33, 95% CI: 1.08-1.63, $P = 0.008$, respectively).

Conclusions:

Use of typical antipsychotics is associated with a dose-dependent increased risk of severe asthma exacerbation. Physicians should thus weight the risk and benefit of prescribing high-dose typical antipsychotics for asthma patients.

Introduction

Asthma is a prevalent airway disease with variable respiratory symptoms and airflow limitations.[1] It is the second most common chronic respiratory disease globally and accounts for 0.88% of all-cause mortality in 2017.[2] Exacerbation of asthma is defined as an episodic and progressive increase in asthma-associated respiratory symptoms, which impair patients' health-related quality of life.[3] Severe exacerbation of asthma leading to emergency department (ED) visits or hospitalization causes human

productivity loss and incurs additional medical costs.[4] Moreover, it increases risk of future exacerbations.[5]

Antipsychotics are used in 3.5% of Taiwan.[6] In addition to treating schizophrenic disorder, antipsychotics are administered for a variety of psychiatric disorders, such as mood disorder, agitation, delirium, and insomnia.[7, 8] Off-label prescriptions of antipsychotics account for 40–75% of all prescriptions in adults.[9] Antipsychotics can be classified into typical and atypical ones based on their affinity to the D2 dopaminergic receptor and the serotonin 5-HT_{2A} receptor, the side effects are different between the two groups of drugs because their affinity to different receptors. [10] In addition to dopaminergic receptor and serotonin receptors, antipsychotics are multipotent drugs that block several neurotransmitter receptors,[10] including the M2 muscarinic receptor, and β_2 adrenergic receptor.[11] The blocking of bronchodilation receptors, such as the β_2 adrenergic, may be associated with acute asthma exacerbation.[12] Crane et al. found a higher risk of asthma-related death and hospital readmission for antipsychotics users.[13] However, this case-control study only analyzed a small number of subjects receiving psychotropic drugs and the enrolled population were limited to people aged 5–45 years in New Zealand during 1981–1987. Most atypical antipsychotics drugs that are used clinically received approval from the Food and Drug Administration after the 1990s.[14] The risk of severe asthma exacerbation with the administration of atypical antipsychotics is still unclear. We hypothesized that the use of antipsychotics is associated with an increase of severe asthma exacerbation leading to ED visits or hospitalization. Using nationwide claims data, we conducted a case-crossover study to validate our hypothesis. We also tested the dose-dependent effect and performed subgroup analyses regarding different classes and receptor functions of antipsychotics.

Methods

Study setting and design

We performed this study using the 2003–2017 Taiwan National Health Insurance Reimbursement Database (NHIRD), which was derived from Taiwan Health and Welfare Data Science Center. The database includes the administrative data of 23 million people and covers 98% of residents in Taiwan. [15] This study used a case-crossover design. We compared the use of antipsychotics and other clinical factors during the period immediately prior to severe asthma exacerbation with that during an earlier control period. The Institutional Review Board of National Cheng Kung University Hospital approved this study before commencement (B-EX-109-026). Informed consent was waived because of the use of de-identified information.

Definition of asthma patients and severe asthma exacerbation

All asthma patients newly diagnosed between January 1, 2003, and December 31, 2016, were identified (Fig. 1A). We defined asthma patients as those who had more than one inpatient or two outpatient visits

within 1 year using the *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis codes 493.xx or ICD-10-CM (Clinical Manifestation) codes J45.x.[15] The accuracy of diagnoses recorded in the NHIRD for asthma has been validated.[16] The first visit was defined as the day of asthma diagnosis. We excluded patients with a diagnosis of asthma between January 1, 2000, and December 31, 2002, to ensure that all the cases were newly diagnosed. Patients with ICD-9 or ICD-10 codes for chronic obstructive pulmonary disease, chronic bronchiolitis, emphysema, and bronchiectasis, those younger than 18 years of age, and those who lacked sex information were also excluded. Every patient must have had at least one asthma-related ED visit or hospitalization during the study period.

Severe asthma exacerbation was defined as an acute exacerbation of asthma resulting in ED visits or hospitalization in combination with the use of short-acting bronchodilators and systemic steroids. To avoid being confounded by previous severe exacerbation, we selected the first episode for analysis. ED visits and hospitalization within 180 days of the day of asthma diagnosis were excluded to avoid confounding from inadequate disease-control-related acute exacerbation at asthma diagnosis.

Case and control periods

Based on previous studies and the elimination half-lives of antipsychotics (**Supplementary Table 1**),[17, 18] we defined the case period as 1 to 14 days prior to severe asthma exacerbation and the control period as 75 to 88 days prior to severe asthma exacerbation (Fig. 1B). These definitions ensured washout of the drug effects. Patients' co-morbidities during the 180 days before the case period were compared with those during the 180 days before the control period to derive the odds ratios (ORs). The use of other medications during the case period were compared with that during the control period. The ICD codes of comorbidities and medications are listed in **Supplementary Table 2** and **Supplementary Table 3**.

Statistical analysis

In order to accommodate the case-crossover design, we used conditional logistic regression analyses to deal with matched pair data. We first conducted a univariable analysis to derive the crude OR of each covariate in the case period versus the control period. Covariates with significant crude ORs ($P < 0.05$) in the univariable analysis were used in the multivariable analysis to obtain the adjusted ORs. To test the robustness of the results, we performed several sensitivity analyses. First, we categorized asthma patients by use of typical antipsychotics, atypical antipsychotics, or both. Second, we examined the dose-dependent effect of antipsychotics by dividing the study cohort into low-dose and medium- to high-dose groups. We defined both groups based on the defined daily dose (DDD).[19] A low dose denoted a dose of less than or equal to 0.25 DDD and a medium to high dose denoted a dose of more than 0.25 DDD.[17] Cochran-Armitage trend test was used to confirm whether the antipsychotics have a dose dependent effect on severe asthma exacerbation. Third, because schizophrenia is the main indication of antipsychotics. We performed the analysis after excluding enrolled subjects with schizophrenia for avoiding the confounding effect of schizophrenia. Fourth, we classified each antipsychotic by its antagonism property on different receptors with the bronchial relaxation function, which include the β_2 adrenergic, M2 muscarinic, D1 dopaminergic, and D2 dopaminergic receptors.[20–23] We defined Ki

value < 100 as higher affinity and Ki value > 100 as lower affinity (**Supplementary Table 4**).^[11] All analyses were performed using SAS software (Version 9.4; SAS Institute, Cary NC, USA) and *P* values were based on two-tail tests.

Results

A total of 18,657 patients from 2003 to 2016 with severe asthma exacerbation resulting in ED visits or hospitalization in combination with the use of short-acting bronchodilators and systemic steroids were included for analysis. Demographic characteristics, comorbidities, and drugs exposure during the case and control periods are shown on Table 1. Most of the patients were female. The mean age was 47.7 years on the event day. Enrolled patients were more likely to have more diagnoses of comorbidities, schizophrenia, pneumonia, and acute upper airway infection in the case period. Moreover, enrolled patients were more likely to use antiplatelet, β -blockers, NSAIDs, antidepressants, antipsychotics, anticholinergic agents, antihistamine, inhaled bronchodilators, and oral bronchodilators in the case period than in the control period (Table 1).

Table 1
Characteristics of patients in the case and control periods.

Characteristics	Number (%)		Conditional logistic regression	
	Case period (<i>n</i> = 18657)	Control period (<i>n</i> = 18657)	Crude OR (95% CI)	<i>P</i> value
Male	5577 (29.9)	5577 (29.9)	-	-
Age, mean (SD)	47.7 (17.9)	47.5 (17.7)		
Comorbidities:				
Heart failure	395 (2.1)	349 (1.9)	2.18 (1.49–3.18)	< 0.001
Ischemic heart disease	931 (5.0)	873 (4.7)	1.62 (1.25–2.10)	< 0.001
Stroke	530 (2.8)	498 (2.7)	1.62 (1.14–2.28)	0.007
GERD	762 (4.1)	671 (3.6)	1.65 (1.34–2.04)	< 0.001
Obesity	77 (0.4)	49 (0.3)	4.11 (1.98–8.52)	< 0.001
Rhinosinusitis	3393 (18.2)	3125 (16.8)	1.44 (1.30–1.60)	< 0.001
Obstructive sleep apnea	51 (0.3)	44 (0.2)	1.64 (0.77–3.46)	0.198
Psychiatric disorder				
Anxiety	166 (0.9)	159 (0.9)	1.21 (0.76–1.92)	0.415
Bipolar disorder	154 (0.8)	146 (0.8)	1.62 (0.81–3.23)	0.174
Depression	747 (4.0)	741 (4.0)	1.08 (0.79–1.47)	0.633
Schizophrenia	148 (0.8)	136 (0.7)	5.00 (1.45–17.27)	0.011
Respiratory infection				
Pneumonia	726 (3.9)	533 (2.9)	2.44 (2.00–2.98)	< 0.001
Acute upper airway infection	8308 (44.5)	7140 (38.3)	2.00 (1.86–2.14)	< 0.001
Medications:				
Cardiovascular drugs				

GERD: gastroesophageal reflux disease; ICS: inhaled corticosteroid, LABA: long-acting β -agonist; LAMA: long-acting muscarinic antagonist; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; SABA: short-acting β -agonist; SAMA: short-acti

	Number (%)		Conditional logistic regression	
Antiplatelet	1184 (6.4)	1019 (5.5)	1.52 (1.32–1.75)	< 0.001
Cardioselective β -blockers	716 (3.8)	660 (3.5)	1.24 (1.04–1.47)	0.015
Non-selective β -blockers	676 (3.6)	553 (3.0)	1.52 (1.29–1.78)	< 0.001
Statins	909 (4.9)	883 (4.7)	1.08 (0.93–1.25)	0.324
Anti-inflammation				
Colchicine	138 (0.7)	147 (0.8)	0.90 (0.67–1.22)	0.492
NSAIDs	5175 (27.7)	3098 (16.6)	2.32 (2.19–2.47)	< 0.001
Metformin	753 (4.0)	721 (3.9)	1.15 (0.96–1.39)	0.133
Psychoactive drugs				
Antidepressants	957 (5.1)	857 (4.6)	1.39 (1.19–1.64)	< 0.001
Lithium	16 (0.1)	13 (0.1)	2.00 (0.50–8.00)	0.327
Antipsychotics	713 (3.8)	601 (3.2)	1.48 (1.25–1.74)	< 0.001
Anticholinergic agents				
Bladder	116 (0.6)	93 (0.5)	1.43 (1.01–2.04)	0.044
Gastrointestinal tract	1442 (7.7)	888 (4.8)	1.86 (1.69–2.05)	< 0.001
Parkinsonism	107 (0.6)	100 (0.5)	1.28 (0.76–2.16)	0.358
Antihistamine				
First generation	3234 (17.3)	1817 (9.7)	2.26 (2.11–2.43)	< 0.001
Second/third generation	4372 (23.4)	2615 (14.0)	2.27 (2.13–2.42)	< 0.001
Inhaled bronchodilators				
SABA	2615 (14.0)	1087 (5.8)	3.25 (2.98–3.54)	< 0.001
SAMA	305 (1.6)	60 (0.3)	6.56 (4.78–9.01)	< 0.001
SABA + SAMA	154 (0.8)	79 (0.4)	2.50 (1.80–3.47)	< 0.001

GERD: gastroesophageal reflux disease; ICS: inhaled corticosteroid, LABA: long-acting β -agonist; LAMA: long-acting muscarinic antagonist; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; SABA: short-acting β -agonist; SAMA: short-acti

	Number (%)		Conditional logistic regression	
LABA	3 (0.02)	0 (0.0)	-	-
LAMA	37 (0.2)	30 (0.2)	1.44 (0.76–2.72)	0.265
LABA + ICS	1575 (8.4)	1217 (6.5)	1.55 (1.41–1.72)	< 0.001
LABA + LAMA + ICS	0 (0.0)	0 (0.0)	-	-
ICS	381 (2.0)	283 (1.5)	1.50 (1.25–1.80)	< 0.001
Oral bronchodilators				
Xanthium	3844 (20.6)	1771 (9.5)	3.40 (3.15–3.66)	< 0.001
Leukotriene receptor antagonists	550 (3.0)	404 (2.2)	1.78 (1.49–2.12)	< 0.001
GERD: gastroesophageal reflux disease; ICS: inhaled corticosteroid, LABA: long-acting β -agonist; LAMA: long-acting muscarinic antagonist; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; SABA: short-acting β -agonist; SAMA: short-acti				

Table 2 shows the results of conditional logistic regression for the risk of severe asthma exacerbation associated with any use of antipsychotics. There were 713 (3.8%) patients with any use of antipsychotics during the case period and 601 (3.2%) patients during the control period. The adjusted OR was 1.27 (95% confidence interval (CI), 1.05–1.54; $P=0.013$). The adjusted ORs of all covariates in multivariable conditional logistic regression are shown in **Supplementary Table 5**. Schizophrenia increased the risk of severe asthma exacerbation (adjusted OR: 5.46; 95% CI: 1.48–20.18; $P=0.011$). After excluding patients with schizophrenia, any use of antipsychotics still increased the risk of severe asthma exacerbation (adjusted OR: 1.29; 95% CI: 1.07–1.57, $P=0.009$) (Table 3).

Table 2
Risk of severe asthma exacerbation by different classes of antipsychotics and doses

Number (%)		Conditional logistic regression					
Characteristics	Case period (<i>n</i> = 18657)	Control period (<i>n</i> = 18657)	Crude OR (95% CI)	<i>P</i> value	Adjusted OR ^a (95% CI)	<i>P</i> value	<i>P</i> for trend
No use of antipsychotics	17944 (96.18)	18056 (96.78)	Ref.		Ref.		
Any use of antipsychotics	713 (3.8)	601 (3.2)	1.48 (1.25–1.74)	< 0.001	1.27 (1.05–1.54)	0.013	
Antipsychotics class ^b							
Typical only	269 (1.44)	193 (1.03)	1.63 (1.31–2.04)	< 0.001	1.40 (1.10–1.79)	0.007	
Atypical only	411 (2.20)	390 (2.09)	1.25 (0.98–1.59)	0.072	1.10 (0.84–1.44)	0.481	
Both	33 (0.18)	18 (0.10)	3.03 (1.40–6.57)	0.005	2.47 (1.09–5.62)	0.031	
Dose							
Low (≤ 0.25 DDD)	604 (3.24)	504 (2.70)	1.47 (1.24–1.74)	< 0.001	1.27 (1.05–1.53)	0.013	0.025
Medium to high (> 0.25 DDD)	109 (0.58)	97 (0.52)	1.57 (1.11–2.21)	0.011	1.47 (1.01–2.15)	0.045	

DDD: defined daily dose; OR: odds ratio.

^a Adjusted for heart failure, ischemic heart disease, stroke, gastroesophageal reflux disease, obesity disorder, rhinosinusitis, psychiatric disorder, schizophrenia, pneumonia, acute upper airway infection, antiplatelet agents, cardioselective β -blocker, non-selective β -blocker, NSAID, anti-psychotics, anti-depressants, bladder anticholinergic agents, gastrointestinal tract anticholinergic agents, first generation anti-histamine, second/third generation anti-histamine, short-acting beta-agonist, short-acting muscarinic antagonist, short-acting beta-agonist plus short-acting muscarinic antagonist, long-acting beta-agonist plus long-acting beta-agonist, long-acting beta-agonist, xanthine inhibitor, leukotriene receptor antagonist.

^b See **Supplementary Table 1**.

Number (%)			Conditional logistic regression				
Dose (typical only)							
Low (≤ 0.25 DDD)	255 (1.37)	184 (0.99)	1.61 (1.28–2.02)	< 0.001	1.37 (1.06–1.76)	0.015	0.006
Medium to high (> 0.25 DDD)	14 (0.08)	9 (0.05)	2.85 (0.96–8.50)	0.060	4.50 (1.36–14.94)	0.014	
Dose (atypical only)							
Low (≤ 0.25 DDD)	326 (1.75)	311 (1.67)	1.27 (0.99–1.63)	0.066	1.11 (0.84–1.46)	0.479	0.652
Medium to high (> 0.25 DDD)	85 (0.46)	79 (0.42)	1.36 (0.91–2.03)	0.134	1.21 (0.78–1.88)	0.385	
DDD: defined daily dose; OR: odds ratio.							
^a Adjusted for heart failure, ischemic heart disease, stroke, gastroesophageal reflux disease, obesity disorder, rhinosinusitis, psychiatric disorder, schizophrenia, pneumonia, acute upper airway infection, antiplatelet agents, cardioselective β -blocker, non-selective β -blocker, NSAID, anti-psychotics, anti-depressants, bladder anticholinergic agents, gastrointestinal tract anticholinergic agents, first generation anti-histamine, second/third generation anti-histamine, short-acting beta-agonist, short-acting muscarinic antagonist, short-acting beta-agonist plus short-acting muscarinic antagonist, long-acting beta-agonist plus long-acting beta-agonist, long-acting beta-agonist, xanthine inhibitor, leukotriene receptor antagonist.							
^b See Supplementary Table 1 .							

Table 3
Risk of severe asthma exacerbation by different classes of antipsychotics and doses after excluding schizophrenia patients

Characteristics	No. (%)		Conditional logistic regression				
	Case period	Control period	Crude OR (95% CI)	P value	Adjusted OR ^a (95% CI)	P value	P for trend
No use of antipsychotics	17900 (96.73)	18008 (97.31)	Ref.		Ref.		
Any use of anti- psychotics	606 (3.3)	498 (2.7)	1.49 (1.26–1.77)	< 0.001	1.29 (1.07–1.57)	0.009	
Antipsychotics class ^b							
Typical only	260 (1.40)	186 (1.01)	1.62 (1.29–2.03)	< 0.001	1.37 (1.07–1.76)	0.012	
Atypical only	326 (1.76)	298 (1.61)	1.32 (1.01–1.71)	0.039	1.17 (0.88–1.56)	0.293	
Both	20 (0.11)	14 (0.08)	1.87 (0.81–4.30)	0.142	1.63 (0.67–3.97)	0.285	
Dose							
Low (≤ 0.25 DDD)	535 (2.89)	441 (2.38)	1.48 (1.25–1.76)	< 0.001	1.28 (1.05–1.55)	0.013	0.018
Medium to high (> 0.25 DDD)	71 (0.38)	57 (0.31)	1.81 (1.17–2.78)	0.007	1.66 (1.04–2.63)	0.034	

DDD: defined daily dose, OR: odds ratio

^a Adjusted for heart failure, ischemic heart disease, stroke, gastroesophageal reflux disease, obesity disorder, rhinosinusitis, psychiatric disorder, schizophrenia, pneumonia, acute upper airway infection, antiplatelet agents, cardioselective β -blocker, non-selective β -blocker, NSAID, anti-psychotics, anti-depressants, bladder anticholinergic agents, gastrointestinal tract anticholinergic agents, first generation anti-histamine, second/third generation anti-histamine, short-acting beta-agonist, short-acting muscarinic antagonist, short-acting beta-agonist plus short-acting muscarinic antagonist, long-acting beta-agonist plus long-acting beta-agonist, long-acting beta-agonist, xanthine inhibitor, leukotriene receptor antagonist.

^b See **Supplementary Table 1**.

No. (%)		Conditional logistic regression					
Dose (typical only)							
Low (≤ 0.25 DDD)	249 (1.35)	181 (0.98)	1.60 (1.27–2.01)	< 0.001	1.37 (1.06–1.76)	0.015	0.006
Medium to high (> 0.25 DDD)	11 (0.06)	5 (0.03)	4.30 (1.15–16.15)	0.031	5.74 (1.33–24.69)	0.019	
Dose (atypical only)							
Low (≤ 0.25 DDD)	271 (1.46)	252 (1.36)	1.30 (0.99–1.70)	0.057	1.15 (0.85–1.55)	0.364	0.478
Medium to high (> 0.25 DDD)	55 (0.30)	46 (0.25)	1.51 (0.92–2.47)	0.107	1.36 (0.80–2.32)	0.261	
DDD: defined daily dose, OR: odds ratio							
^a Adjusted for heart failure, ischemic heart disease, stroke, gastroesophageal reflux disease, obesity disorder, rhinosinusitis, psychiatric disorder, schizophrenia, pneumonia, acute upper airway infection, antiplatelet agents, cardioselective β -blocker, non-selective β -blocker, NSAID, anti-psychotics, anti-depressants, bladder anticholinergic agents, gastrointestinal tract anticholinergic agents, first generation anti-histamine, second/third generation anti-histamine, short-acting beta-agonist, short-acting muscarinic antagonist, short-acting beta-agonist plus short-acting muscarinic antagonist, long-acting beta-agonist plus long-acting beta-agonist, long-acting beta-agonist, xanthine inhibitor, leukotriene receptor antagonist.							
^b See Supplementary Table 1 .							

The risk of severe asthma exacerbation by different classes of antipsychotics and doses is shown on lower part of Table 2. Use of typical antipsychotics was associated with an increased risk of severe asthma exacerbation (adjusted OR: 1.40, 95% CI: 1.10–1.79, $P=0.007$). In contrast, use of atypical antipsychotics did not increase the risk (adjusted OR: 1.10, 95% CI: 0.84–1.44, $P=0.481$). Simultaneously use both typical and atypical antipsychotics had higher risk of asthma exacerbation than use one of them (adjusted OR: 2.47, 95% CI: 1.09–5.62, $P=0.031$). A dose-dependent effect was also found in the use of any class of antipsychotics. The effect was obvious for the use of typical antipsychotics but not statistically significant for atypical antipsychotics (in the test for trend, any class of antipsychotics: $P=0.025$, typical antipsychotics: $P=0.006$; atypical antipsychotics: $P=0.652$). After excluding patients with schizophrenia, the result of analysis is similar to the result of analysis for all enrolled patients. Use of typical antipsychotics was still associated with increased risk of severe asthma exacerbation with dose-dependent effect, but use of atypical antipsychotics was not (for typical antipsychotics: adjusted OR:

1.37, 95% CI: 1.07–1.76, $P = 0.012$; for atypical antipsychotics: adjusted OR: 1.17, 95% CI: 0.88–1.56, $P = 0.293$) (Table 3).

Table 4 shows the risk of severe asthma exacerbation stratified by different receptor functions of antipsychotics. Agents that block the M2 muscarinic receptor and the D2 dopaminergic receptor are associated with increased risk of severe asthma exacerbation (adjusted OR: 1.39, 95% CI: 1.10–1.76, $P = 0.007$ and adjusted OR: 1.33, 95% CI: 1.08–1.63, $P = 0.008$, respectively).

Table 4
Risk of severe asthma exacerbation of antipsychotics with high blocking affinity of receptor

Characteristics	Number (%)		Conditional logistic regression			
	Case period	Control period	Crude OR (95% CI)	P value	Adjusted OR ^a (95% CI)	P value
No antipsychotics use	17927	18037	Ref.		Ref.	
Antipsychotics with high blocking affinity ^{b,c}						
β2 adrenergic receptor	302 (1.7)	276 (1.5)	1.37 (0.98–1.92)	0.064	1.25 (0.87–1.81)	0.227
M2 muscarinic receptor	442 (2.4)	356 (1.9)	1.60 (1.29–1.99)	< 0.001	1.39 (1.10–1.76)	0.007
D1 dopaminergic receptor	391 (2.1)	357 (1.9)	1.34 (1.04–1.73)	0.025	1.17 (0.88–1.55)	0.283
D2 dopaminergic receptor	535 (2.9)	440 (2.4)	1.52 (1.26–1.84)	< 0.001	1.33 (1.08–1.63)	0.008
^a Adjusted for heart failure, ischemic heart disease, stroke, gastroesophageal reflux disease, obesity disorder, rhinosinusitis, psychiatric disorder, schizophrenia, pneumonia, acute upper airway infection, antiplatelet agents, cardioselective β-blocker, non-selective β-blocker, NSAID, anti-psychotics, anti-depressants, bladder anticholinergic agents, gastrointestinal tract anticholinergic agents, first generation anti-histamine, second/third generation anti-histamine, short-acting beta-agonist, short-acting muscarinic antagonist, short-acting beta-agonist plus short-acting muscarinic antagonist, long-acting beta-agonist plus long-acting beta-agonist, long-acting beta-agonist, xanthine inhibitor, leukotriene receptor antagonist.						
^b High blocking affinity is defined as Ki value < 100 (see Supplementary Table 4).						
^c Antipsychotics without Ki (inhibitory constant) value were excluded from analysis.						

Discussion

Although previous studies have shown that the use of antipsychotics at the time of hospital admission increases the risks of asthma-related death and hospital readmission,[13] the association between the use of antipsychotics and severe asthma exacerbation has not been investigated using a nationwide asthma population. The effects of atypical antipsychotics on severe asthma exacerbation have not been examined. In this case-crossover study, we analyzed 18,657 newly diagnosed asthma patients with severe exacerbation leading to ED visits or hospitalization. Using multivariable conditional logistic regression, we found that use of antipsychotics is associated with increase of the risk of severe asthma exacerbation (adjusted OR: 1.27). This result was not confounded by respiratory infection, schizophrenia, use of NSAIDs or non-selective β -blockers, and different types of inhaled bronchodilator prescription. In the subgroup analysis, use of typical antipsychotics significantly increased the risk of severe asthma exacerbation by 40%. Furthermore, there was a dose-dependent effect of antipsychotics, especially of typical antipsychotics on severe exacerbation of asthma. Analysis for use of atypical antipsychotics did not show an increased risk of severe asthma exacerbation. We thus tentatively conclude that the use of typical antipsychotics is associated with a dose-dependent increased risk of severe asthma exacerbation.

We found that the use of typical antipsychotics led a higher risk of severe asthma exacerbation (adjusted OR: 1.40), whereas the use of atypical antipsychotics did not. This finding is consistent with different adverse events among typical and atypical antipsychotics users. The use of typical antipsychotics is more likely to bring about extrapyramidal symptoms and the use of atypical antipsychotics is often associated with weight gain and metabolic disturbance.[24] A possible explanation for the discordance of side effects between these two groups of drugs is that typical antipsychotics have higher affinity to the dopaminergic receptor and lower affinity to the serotonin receptor compared to those for atypical agents. [10] The higher antipsychotic affinity to specific receptors is associated with a higher risk of different side effects.[25]

We found that simultaneous use of typical and atypical antipsychotics increases risk of severe asthma exacerbation compared to the use of a mono-drug therapy. Combination of two antipsychotics is a widely used strategy for treatment-resistant schizophrenia,[26] and combination of typical and atypical antipsychotics is the most common management in real-world practice.[27] Compare with monotherapy, several studies have reported that combination therapy is associated with increase adverse events and mortality rate.[28–31] Although a recent meta-analysis did not show different risk of serious adverse events between combination antipsychotics and monotherapy, the quality of evidence was very low.[32]

Antipsychotics block the β_2 adrenergic, M2 muscarinic, D1 and D2 dopaminergic receptors, which are found in human airway smooth muscle with the function of bronchial relaxation. Blocking these bronchodilation receptors increases airway smooth muscle tone and induces muscle spasms, [20–23] causing severe asthma exacerbation. The results stratified by different receptor functions of antipsychotics in our study showed that there were higher risks of severe asthma exacerbation for antipsychotics that function on the M2 muscarinic and D2 dopaminergic receptors. A plausible

explanation is that most antipsychotics have higher affinities on the M2 muscarinic and D2 dopaminergic receptors than the β_2 adrenergic receptor (**Supplementary Table 4**). Blocking the D2 dopaminergic receptor could also induce dystonia of the airway,[33] causing acute exacerbation of an airway disease.

In this study, we found that schizophrenia increased the risk of severe asthma exacerbation. Patients with schizophrenic disorder usually have low adherence to asthma treatment and adopt risky health behaviors such as smoking.[34] Including these patients in the analysis might bias the results. However, the magnitude of the effect was not altered after excluding patients with schizophrenia (Table 3).

Several limitations must be acknowledged in our study. First, the claims data did not include important information such as disease severity and pulmonary function data and we did not take different phenotypes of asthma into consideration. Nevertheless, we adjusted for the use of different inhaled bronchodilators or their combinations, which could be regarded as a surrogate for asthma severity. Consequently, the results were not significantly biased. Second, the diagnoses of asthma and its acute exacerbation should be based on medical history and physical examination instead of ICD codes only. Nevertheless, the accuracy of diagnostic record for asthma in NHIRD had been validated.[16] We further defined newly diagnosed asthma patients as those who had more than one inpatient or two outpatient visits and excluded subjects with the same diagnosis within the prior 2 years. Severe asthma exacerbation was also defined as an acute exacerbation leading to ED visits or hospitalization in combination with the use of short-acting bronchodilators and systemic steroids. Such strict definitions strengthen the validity of our results. Third, adherence to antipsychotics and other medications could not be confirmed using the claims data. Nevertheless, our study used a case-crossover design, in which drug compliance during the case and control period was supposed to be the same. This factor would not significantly affect the results. Forth, we did not include smoking status into the regression model because NHIRD lacks information on smoking status. However, in our case crossover study design, the time interval between the control period and the case period is 60 days, and the smoking status of each enrolled subject may not change in the short period of time. About 70% of enrolled patient in our study cohort were female. The smoking prevalence of women over 18 years old in Taiwan was 3.9–5.5% during the enrolled period of this study.[35] In our study, the impact of smoking on asthma severe exacerbation might be small.

Conclusions

In this nationwide population-based cohort study, patients with asthma showed a dose-dependent increase in the risk of severe asthma exacerbations when receiving antipsychotics. The effect was more significant for patients receiving typical antipsychotics than atypical antipsychotics. Physicians should thus weight the risk and benefit of prescribing high-dose typical antipsychotics for asthma patients.

Abbreviations

CI: Confidence interval; CM: Clinical manifestation; DDD: Defined daily dose; ED: Emergency department; ICD-9: International Classification of Diseases, Ninth Revision; NHIRD: National health insurance reimbursement database; OR: odds ratio.

Declarations

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Author contributors

Chin-Wei Kuo and Sheng-Hsiang Lin conceptualized and designed the study. Chin-Wei Kuo, Yu-Fen Shih and Xin-Min Liao assisted with data collection. Chin-Wei Kuo, Szu-Chun Yang and Sheng-Hsiang Lin were in charge of data analysis and interpretation. Chin-Wei Kuo and Szu-Chun Yang drafted the manuscript. Sheng-Hsiang Lin, Szu-Chun Yang and Yu-Fen Shih revised the manuscript critically for important intellectual content. All of the authors approved the final version to be published.

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Availability of data and materials

All the data in this study are available to others if the data intend to be used for scholarly purposes such as a systematic review. The data are not publicly available because the use of the National Health Insurance Research Database is limited to research purposes only.

Ethics approval and consent to participate

The study was approved by the local ethics committee before commencement (The Institutional Review Board of National Cheng Kung University Hospital, IRB number:B-EX-109-026). Informed consent was waived because of the use of de-identified information.

Consent for publication

Not applicable.

Competing interests

All authors declare no conflicts of interest.

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Figures

a

b

Figure 1

Algorithm for subject enrollment and timeline for case crossover study. a. Inclusion algorithm for severe asthma exacerbation; b. Timeline for the case and control periods. COPD, chronic obstructive pulmonary disease; ED, emergency department.

Supplementary Files

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