ORIGINAL ARTICLE

Use of antipsychotics and the risk of acute respiratory failure among adults: A disease risk score-matched nested case-control study

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Aims: Evidence on acute respiratory failure (ARF) from antipsychotics is scant, and only 1 population-based study examined this drug safety issue in chronic obstructive pulmonary disease patients. Antipsychotics have been frequently prescribed off-label in adults, but whether antipsychotic use carries an increased ARF risk among adult patients is uncertain.

Methods: We adopted a nested case-control study analysing 716 493 adults aged ≥ 20 years, identified from the Taiwan nationwide healthcare claims records between January 2000 and December 2013. Among the study cohort, 7084 adults with ARF and 12,785 disease risk scored-matched randomly selected controls were analysed. Multivariable logistic regression models were employed to estimate odds ratios of ARF with antipsychotic usages.

Results: Current, recent, and recent past use of antipsychotics was associated with a 2.33-fold (95% confidence interval [CI] = 2.06–2.64), 1.79-fold (95% CI = 1.43–2.25) and 1.41-fold (95% CI = 1.20–1.66) increased risk of ARF, respectively, compared with nonuse, while antipsychotics discontinued >90 days carried no risk. A dose-dependent association was observed with current therapy of antipsychotics (test for trend, $P < .001$), in which antipsychotic use at >1 defined daily dose yielded the highest risk of 6.53-fold (95% CI = 3.33–12.79). The findings were robust to using carbamazepine as an active comparator.

Conclusion: Antipsychotic use was associated with an increased risk of ARF in adult patients. The risk was dose-dependent and markedly higher with current use of antipsychotic agents at doses of 1 defined daily dose and above, $<10\%$ of this cohort. Physicians should be vigilant about any respiratory symptoms in patients currently receiving antipsychotics at such dose.

KEYWORDS

acute respiratory failure, antipsychotics, disease risk score, drug safety, nested case-control study

Abbreviations: ARF, acute respiratory failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DDD, defined daily dose; DRS, disease risk score; ER, emergency room; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICU, intensive care unit; LHID, Longitudinal Health Insurance Database; OR, odd ratios.

The authors confirm that the PI for this study is Meng-Ting Wang. This study was a deidentified claims database-based study; accordingly, there was no direct clinical responsibility needed for patients.

1 | INTRODUCTION

Antipsychotic agents are among the most frequently prescribed classes of medications,¹ which are indicated for treatment of schizophrenia² and bipolar disorder³ and prescribed as an adjunctive pharmacotherapy for major depression.⁴ However, >50% of antipsychotics are used beyond the approved indications,¹ including short-term treatment of neuropsychiatric symptoms in dementia⁵ and for aggression in autism spectrum disorders,⁶ supportive treatment for obsessive-compulsive disorder,⁷ and anxiety as well as insomnia.⁸ The widespread usages of antipsychotic agents have raised concerns about their adverse side effects, including sudden cardiac death,⁹ acute kidney disease¹⁰ and metabolic disease¹¹ as well as overall mortality.¹²

In addition to the above-mentioned adverse effects, severe adverse respiratory events from antipsychotic therapy have been documented, despite scant population-based evidence. Case reports had documented extreme difficulty breathing, acute respiratory distress or acute respiratory failure (ARF) within several hours to 10 days of taking typical^{13–18} or atypical^{13,17–23} antipsychotics with normal^{13–18,21,22} or high dose.^{19,20,23} Despite these case reports, only 1 population-based case-crossover study had tied ARF to antipsychotic use in patients with chronic obstructive pulmonary disease (COPD).²⁴ Nevertheless, the population-based evidence²⁴ is restricted to COPD patients, and consequently it is unclear whether or not general adults receiving antipsychotics could carry the risk of ARF. In fact, several antipsychotic-related ARF cases were reported from patients without any underlying respiratory diseases,^{14,18,20,23} suggesting a potential ARF risk for all users of antipsychotics. Furthermore, due to the nature of the previously employed case-crossover design,²⁴ the adverse respiratory effect from antipsychotic agents was assumed to be acute and brief, which also awaits to be verified.

In the present study, we, accordingly, aimed to conduct a disease risk score-matched nested case-control study to evaluate use of antipsychotics in relation to the risk of ARF in a general adult population, focusing on timing, duration and dose of antipsychotic use.

2 | METHODS

2.1 | Data source

This study analysed the Longitudinal Health Insurance Database (LHID) between 1 January 2000 and 31 December 2013, which is a sub-dataset of the Taiwan National Health Insurance Research Database that is built based on the nationwide compulsory health insurance claims for >99% of the entire Taiwanese population. The LHID is constructed based on the medical and pharmacy claims data of 1 million randomly-selected beneficiaries in the National Health Insurance Research Database, including all medical procedures, diagnoses, and prescribed medications from outpatient, inpatient and emergency care settings. The records in the database are regularly

What is already known about this subject

- Antipsychotics are among the most frequently prescribed classes of medications worldwide, and >50% of antipsychotics have been prescribed off-label in adults.
- Acute respiratory failure (ARF) from antipsychotics has been documented, despite evidence limited in case reports and 1 observational study of chronic obstructive pulmonary disease patients.

What this study adds

- Use of antipsychotic agents was associated with an increased risk of ARF in general adults.
- Current use of antipsychotics was associated with a >2-fold increased risk of ARF, and the risk was elevated to >6-fold with antipsychotics received at >1 defined daily dose.

accredited by the Bureau of National Health Insurance,²⁵ and have been reported to be of high quality and accuracy regarding disease diagnosis codes and medication records.^{26–28} The data of LHID are representative to the entire Taiwanese inhabitants, and have been analysed to evaluate respiratory-related adverse drug reactions.²⁹ All of the identifiers in the LHID are double encrypted, and this study was exempt from a full review of the Institutional Review Board of Tri-service General Hospital National Defense Medical Center (B-104-16).

2.2 | Study cohort identification

We assembled a population-based cohort consisting of all individuals aged ≥ 20 years from 1 January 2001 to 31 December 2012. We defined cohort entry date as an individual's 20th birthday occurring between 1 January 2001 and 30 December 2012 or the date of 1 January 2001, on which an individual had turned >20 years. To ensure measuring incident outcomes and identifying new users of antipsychotics, we excluded patients with any diagnosis of ARF, receipt of any antipsychotics, or without a continuous enrolment in the NHI in the year before cohort entry. Each member of the cohort was followed from the cohort entry date till the earliest of the following events: first hospitalization or emergency room (ER) visit of ARF, withdrawal from the NHI, death, or the study end date (31 December 2013). Mortality was determined using in-hospital mortality data and permanent disenrollment status of the NHI,³⁰ which has been validated with high accuracy.²⁶

2.3 | Case identification and control selection

A nested case-control analysis was performed within the study cohort. We adopted this analytical approach primarily owing to the time-varying nature of antipsychotic use and low incidence rate of ARF. There are several advantages for adopting a nested case-control design over a conventional case-control design, such as reduction in selection bias and a similar follow-up time period for both cases and matched controls. Cases were defined by a hospital or an ER visit for ARF based on the primary or secondary diagnosis of acute respiratory failure (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 518.81), acute respiratory distress (ICD-9-CM code 518.82), acute and chronic respiratory failure (ICD-9-CM code 518.84), or other respiratory abnormalities (ICD-9-CM code 786.09), necessitating intubation or mechanical ventilation. We only examined the first ARF event during follow-up and referred the ARF hospital or ER admission date as the index date. To avoid capturing ARF from other causes, we excluded patients who had a diagnosis of bacteraemia/sepsis/shock, cardiogenic pulmonary oedema, pulmonary insufficiency following trauma and surgery, head or thoracic injuries within the 90 days before or on the ARF occurring date, or receipt of any solid organ or bone marrow transplantations during follow-up (detailed in Table S1).

Each case was matched with up to 2 randomly-selected controls within the risk sets, who were all eligible patients without the severe respiratory event at the time when each ARF case occurred, by cohort entry date (± 180 days), disease risk score ($\text{DRS} \pm 0.01$) which predicts the occurrence of ARF, and presence or absence of heart failure, COPD and pneumonia, which were measured in the year preceding the index date. The use of DRS to match cases with controls in a nested case-control study could lead to a better statistical precision than does matching on specific variables.³¹ The estimation of DRS was detailed in Method S1. Controls were assigned the same index date as the corresponding cases and applied with the same exclusion criteria as set for the cases.

2.4 | Antipsychotic exposure

We examined all antipsychotic prescription refill records for both cases and controls in the year before the index date. Specifically, antipsychotic exposure was classified into current use (1–14 days before the index date), recent use (15–30 days), recent past use (31–90 days), past use (91–180 days), and remote use (181–365 days) according to the time gap from the end of the most proximal antipsychotic prescription to the index date. We additionally separated patients into new users, who did not have any other antipsychotic prescriptions in the year before the index date, and prevalent users otherwise. We further measured type of antipsychotics (typical and atypical), daily dose, duration and route of administration (oral and any injections) of antipsychotic therapy. The average daily dose of antipsychotics was standardized according to defined daily dose (DDD), and further categorized into ≤ 0.25 , 0.26–0.5, 0.51–1.0 and >1.0 DDD. Duration of

antipsychotic therapy was assessed with the permission of a 7-day grace period, and grouped into 1–14 days, 15–30 days, 31–90 days and >90 days of continuous use. Nonuse of antipsychotics served as the primary reference group, but an active comparison was employed in the sensitivity analyses.

2.5 | Covariate measurement

We considered the following potential confounders that may associate with antipsychotic use or occurrence of ARF, detailed in Table S1: (i) comorbidities (such as cardiovascular diseases, pulmonary diseases, psychiatric conditions, diabetes mellitus, renal failure, chronic liver disease, sleep apnoea, neuromuscular diseases and spinal cord injuries); (ii) presence of hospital admission (classified as none, intensive care units [ICUs], and other admissions); and (iii) co-medications (such as central nervous system drugs, cardiovascular drugs, anticholinergics, respiratory medications, muscle relaxants and respiratory failure-related agents). Comorbidities and the other 2 types of factors were measured in the year and in the 6 months prior to cohort entry, respectively, all of which were then included in a logistic regression model to estimate the DRS of ARF, as detailed in Method S1. We also measured these factors in the year preceding the index date for comorbidities, in the 6 months for comedications, and in the 3 months for hospital admission, including ICU.

2.6 | Statistical analysis

We performed logistic regressions to estimate odd ratio (ORs) and 95% confidence interval (CI) for the risk of ARF with antipsychotic use. We employed logistic regression models instead of conditional logistic regression analysis because both methods yielded similar results, as shown in the results of sensitivity analyses, but the conditional regression analysis caused a significant drop in sizes due to no variation in antipsychotic use within multiple pairs when conducting subgroup or stratified analyses. We adjusted for the covariates listed above with standardized difference >0.1 in the multivariable analyses, which represents meaningful imbalance between groups. Data sets were prepared by SAS, version 9.2 (SAS Institute) and analysed by STATA, version 11 (STATA Corp).

2.7 | Additional analyses

Several prespecified additional analyses were performed. Exposures to opioids (>1 DDD) and sennosides were analysed as the positive and negative control agent, respectively. Opioids were chosen as a positive control agent because of their tie with ARF.^{32,33} Multiple sensitivity analyses were conducted to assess the robustness of the reported findings for current use of antipsychotics among a general adult population. First, we performed a case-crossover study that self-compared the use of antipsychotics in the risk period and in the

control period for each of the identified cases of ARF in order to address potential selection bias and time-invariant confounding (detailed in supplementary method S2 and Figure S1). Second, current use of carbamazepine was additionally treated as a reference category for mitigating confounding by indication bias. We chose carbamazepine because it is used as an adjunctive therapy for schizophrenia³⁴ and an alternative therapy for bipolar disorder,³⁵ and the drug use at usual dose is not linked with ARF.³⁶ We did not specify the use of carbamazepine for epilepsy because the drug was mainly used as off-label, such as agitation.³⁷ Third, we performed stratified analyses by presence or absence of COPD, asthma and heart failure. Fourth, we repeated analyses with only cases of ARF requiring an ICU admission in order to investigate severe ARF associated with antipsychotic use. Fifth, we excluded patients with major risk factors of ARF, such as those with pneumonia, aspiration, pulmonary embolism and pulmonary oedema before the index date; those with severe psychiatric disease including schizophrenia and bipolar disorder; and those with severe infection, such as meningitis, human immunodeficiency virus/acquired immune deficiency syndrome, acute bronchitis and tuberculosis in the 1 year prior to the index date. These 3 exclusion criteria were separately implemented in order to capture idiopathic ARF, to minimize confounding by disease severity, and to address confounding by severe infection, respectively. Sixth, to avoid observing antipsychotic use for treatment of delirium, a potential pre-symptom of ARF, we excluded patients with any delirium diagnosis, admission to ICU or initiation of benzodiazepine agents, which can be used for seizure-related or alcohol withdrawal delirium,³⁸ in the 3 months before the index date. To further address the protopathic bias, we conducted a lag-time approach analysis by excluding patients using antipsychotics within 7 days preceding the index date. Seventh, to assess the possibility of confounding by comedications that have been reported to cause severe respiratory events,³⁹ we excluded patients who received these medications. Eighth, we adopted different multivariable analyses, including adoption of conditional logistic regressions and adjustment for all covariates listed in Table 1. Finally, we employed a rule-out approach⁴⁰ to evaluate the magnitude of the strength that an unmeasured confounder is required to move the observed OR toward the null.

2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

We included the study cohort of 716 493 adult patients, who had a mean (standard deviation) age of 38.8 (16.3) years and had no prior ARF diagnosis nor previous antipsychotic prescription records at

cohort entry (Figure 1). The reasons for truncation during follow-up are detailed in Table S2; for example, 4.4% of the study cohort being censored due to mortality. The study cohort was followed up for a mean of 8.0 years, generating 5 733 489 person-years. Of these, we identified 18 158 new cases of ARF, with a corresponding incidence rate of 3.17 per 1000 person-years. After matching, there were 12 775 cases and 23 310 DRS-matched randomly selected controls. A total of 7084 cases and 12 785 matched controls were included for analysis with implementation of the exclusion criteria.

All characteristics between cases and controls were balanced at baseline (Table 1). Additionally, during follow-up, the balanced conditions remained for the majority of the covariates, while some were significantly higher among cases than controls, such as presence of stroke, for which statistical adjustment was adopted.

Table 2 shows that current use of antipsychotics yielded the highest risk of ARF (adjusted OR = 2.33 [95% CI = 2.06, 2.64]; $P < .001$), followed by recent (adjusted OR = 1.79 [95% CI = 1.43, 2.25]; $P < 0.001$) and recent past use (adjusted OR = 1.41 [95% CI = 1.20, 1.66]; $P < 0.001$), albeit no increased risk for past and remote use.

The associations of various antipsychotic usages with risk of ARF among current users were further scrutinized (Table 3). Current use of typical, atypical antipsychotics, and both types was associated with a 1.90-fold (95%CI = 1.63, 2.22; $P < .001$), 3.04-fold (95% CI = 2.48, 3.73; $P < .001$), and 4.95-fold (95% CI = 2.67, 9.18; $P < .001$) increased risk of ARF, respectively. Additionally, there seemed to exhibit a marginal duration-response trend (test for trend, $P = .070$). The risk of ARF escalated with an increasing daily dose level of antipsychotics (test for trend, $P < .001$), with the risks ranging from 1.96-fold to 6.53-fold from the lowest to the highest dose. Among recent and recent past antipsychotic users, we also observed the dose-dependent effects and duration-response associations (Table 4).

As expected, use of opioids was associated with an increased ARF risk (Table S3), and sennoside use was not found to increase the risk (Table S4). Our findings were robust to the results of the sensitivity analyses (Figure 2). Particularly, the observed risk persisted in the case-crossover analysis (Tables S5, S6) and with the employment of current carbamazepine use as the reference group. The risk remained significant, irrespective of the presence or absence of COPD, asthma and heart failure (Figure 2). The existence of an unmeasured confounder could fully account for our findings if it increased the risk of ARF by 6.0 times, and was 10.4 times more prevalent in antipsychotic users than nonusers (Figure S2).

4 | DISCUSSION

This large nested case-control study of 716 493 adults revealed a >2-fold increased risk of ARF with current use of antipsychotics compared with nonuse, gradually diminished with recent and recent past antipsychotic therapy. There was a dose-dependent risk of ARF with current use of antipsychotics, in which high-dose was associated with

TABLE 1 Characteristics of acute respiratory failure cases and matched controls

Characteristics	At baseline ^a					During follow-up ^b				
	Cases (n = 7084)		Controls (n = 12 785)		Standardized difference	Cases (n = 7084)		Controls (n = 12 785)		Standardized difference
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age at cohort entry (y)	61.9	14.5	61.1	14.0	0.052	61.9	14.5	61.1	14.0	0.052
	n	%	n	%		n	%	n	%	
Sex, male	4102	57.9	7532	58.9	0.020	4102	57.9	7532	58.9	0.020
Hospital admission										
None	6123	86.4	11 296	88.4	0.058	5795	81.8	11 268	88.1	0.178
ICU	73	1.0	100	0.8	0.026	220	3.1	205	1.6	0.099
Other admission	888	12.5	1389	10.9	0.052	1069	15.1	1312	10.3	0.145
Comorbidities										
Cardiovascular disease										
Hypertension	2503	35.3	4122	32.2	0.065	3665	51.7	6061	47.4	0.087
Ischaemic heart disease	894	12.6	1484	11.6	0.031	1455	20.5	2234	17.5	0.078
Stroke	628	8.9	882	6.9	0.073	1409	19.9	1804	14.1	0.154
Arrhythmia	400	5.7	663	5.2	0.020	768	10.8	1027	8.0	0.096
Heart failure	172	2.4	297	2.3	0.007	637	9.0	941	7.4	0.060
Peripheral vascular disease	202	2.9	350	2.7	0.007	414	5.8	479	3.8	0.098
Pulmonary embolism	0	0	2	0.02	0.018	33	0.5	11	0.1	0.072
Pulmonary disease										
COPD	768	10.8	1437	11.2	0.013	1429	20.2	2253	17.6	0.065
Asthma	460	6.5	824	6.5	0.002	708	10.0	977	7.6	0.083
Pneumonia	173	2.4	323	2.5	0.005	961	13.6	1434	11.2	0.071
Pulmonary oedema	6	0.1	5	0.04	0.018	79	1.1	47	0.4	0.087
Aspiration	0	0	0	0	NA	89	1.3	56	0.4	0.089
Chronic respiratory failure	0	0	0	0	NA	14	2.0	2	0.02	0.056
Psychiatric disease										
Anxiety	556	7.9	1002	7.8	<0.001	699	9.9	1206	9.4	0.015
Depression	116	1.6	228	1.8	0.011	330	4.7	417	3.3	0.072
Dementia	47	0.7	44	0.3	0.045	509	7.2	691	5.4	0.073
Bipolar disorder	11	0.2	14	0.1	0.013	47	0.7	28	0.2	0.067
Schizophrenic disorder	4	0.1	7	0.1	0.001	53	0.8	18	0.1	0.091
Delirium	2	0.03	4	0.03	0.002	66	0.9	38	0.3	0.081
Diabetes mellitus	1247	17.6	1822	14.3	0.092	1907	26.9	2751	21.5	0.126
Chronic liver disease	631	8.9	1159	9.1	0.006	735	10.4	985	7.7	0.093
Renal failure	178	2.5	219	1.7	0.056	688	9.7	615	4.8	0.190
Parkinson's disease	69	1.0	70	0.6	0.049	272	3.8	279	2.2	0.097
Seizure	65	0.9	91	0.7	0.023	165	2.3	132	1.0	0.101
Alcoholism	22	0.3	36	0.3	0.005	244	3.4	243	1.9	0.096
Neuromuscular diseases and spinal injuries	25	0.4	27	0.2	0.027	59	0.8	42	0.3	0.066
Acute pancreatitis	10	0.1	23	0.2	0.010	59	0.8	33	0.3	0.078
Cancer	8	0.1	12	0.1	0.006	123	1.7	85	0.7	0.098

TABLE 1 (Continued)

Characteristics	At baseline ^a					During follow-up ^b				
	Cases (n = 7084)		Controls (n = 12 785)		Standardized difference	Cases (n = 7084)		Controls (n = 12 785)		Standardized difference
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Sleep apnea	5	0.1	4	0.03	0.017	28	0.4	47	0.4	0.004
GERD	1	0.01	3	0.02	0.007	411	5.8	535	4.2	0.074
Medication use										
CNS depressive drugs										
Antihistamines										
First generation	2834	40.0	5365	42.0	0.040	3395	47.9	5480	42.9	0.102
Second/third generation	1081	15.3	2040	16.0	0.019	1842	26.0	3249	25.4	0.013
Antidepressants										
TCA	193	2.7	367	2.9	0.009	411	5.8	473	3.7	0.099
SSRI/SNRI	65	0.9	86	0.7	0.028	303	4.3	380	3.0	0.070
Others	3	0.04	2	0.02	0.016	90	1.3	85	0.7	0.062
BZDs/non-BZDs	2253	31.8	4006	31.3	0.010	3012	42.5	4478	35.0	0.154
Antidopaminergics	1062	15.0	1854	14.5	0.014	1819	25.7	2512	19.7	0.144
Barbiturates	292	4.1	534	4.2	0.003	200	2.8	338	2.6	0.011
Opioids analgesics	195	2.8	334	2.6	0.009	1001	14.1	1095	8.6	0.176
Anaesthetics	2	0.03	8	0.1	0.016	75	1.1	65	0.5	0.062
Cardiovascular drugs										
Antiplatelets	1220	17.2	1871	14.6	0.071	2204	31.1	3405	26.6	0.099
Beta-blockers										
Cardiovascular selective	734	10.4	1228	9.6	0.025	932	13.2	1588	12.4	0.022
Noncardiovascular selective	663	9.4	1080	8.5	0.032	1020	14.4	1452	11.4	0.091
Statins	180	2.5	244	1.9	0.043	737	10.4	1419	11.1	0.022
Anticholinergic agents										
Gastrointestinal antispasmodics	1631	23.0	2934	23.0	0.002	1603	22.6	2445	19.1	0.086
Bladder antimuscarinics	171	2.4	295	2.3	0.007	275	3.9	386	3.0	0.047
Antiparkinsonian	42	0.6	44	0.3	0.036	162	2.3	242	1.9	0.028
Others	4	0.1	8	0.1	0.003	35	0.5	32	0.3	0.040
Respiratory medications										
Methylxanthine	181	2.6	344	2.7	0.008	520	7.3	658	5.2	0.091
SABAs	126	1.8	169	1.3	0.037	721	10.2	694	5.4	0.178
SAMAs	58	0.8	73	0.6	0.030	597	8.4	554	4.3	0.168
ICS	52	0.7	104	0.8	0.009	349	4.9	340	2.7	0.119
LABAs	12	0.2	14	0.1	0.016	274	3.9	282	2.2	0.097
LTRAs	4	0.1	8	0.1	0.003	42	0.6	38	0.3	0.044
LAMAs	0	0	0	0	NA	102	1.4	106	0.8	0.058
NSAIDs	3607	50.9	6729	52.6	0.034	4187	59.1	7083	55.4	0.075
Muscle relaxants	1473	20.8	2831	22.1	0.033	1520	21.5	2533	19.8	0.041
Adverse respiratory event-related drugs	796	11.2	1254	9.8	0.047	1287	18.2	1654	12.9	0.145
Amiodarone	20	0.3	42	0.3	0.008	224	3.2	144	1.1	0.141

Abbreviations: SD, standard deviation; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; CNS, central nervous system; TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin–norepinephrine reuptake inhibitors; BZDs, benzodiazepines; SABAs, short-acting β_2 agonists; SAMAs, short-acting muscarinic antagonists; ICS, inhaled corticosteroids; LABAs, long-acting β_2 agonists; LAMAs, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; NSAIDs, nonsteroidal anti-inflammatory drugs; NA, not available.

^aAll comorbidities and hospital admission were measured in the year and comedications in the 6 months before entry date.

^bAll comorbidities were measured in the year, comedications in the 6 months, and hospital admission in the 3 months before index date.

FIGURE 1 Flow diagram illustrating case and control selection. ARF, acute respiratory failure

a >6-fold increased risk but only <10% of patients received this high dose of antipsychotic agents. The findings persisted when adopting a case-crossover analysis and performing an active comparison with carbamazepine, and remained significant across other sensitivity analyses performed to address different types of confounding and bias. If our observed association represents a true causal effect, 1 severe ARF event could occur for every 571 (464–717) patients currently treated with antipsychotic agents for 1 year. This figure of number needed to harm reflects a modest effect size. Accordingly, given that antipsychotics are among the most prescribed classes of medications, and that ARF is a life-threatening event, the reported respiratory adverse event associated with antipsychotic use indeed needs particular attention in present clinical practice.

Our study contributed new insights to the severe adverse respiratory effects of antipsychotic agents. To our knowledge, we are the

first to identify that timing and dose of antipsychotic therapy are strong effect modifiers of the therapy-related severe respiratory adverse events. Based on the investigation of recency of therapy, we observed a >2-fold increased risk of ARF under current therapy of antipsychotics, which is in line with the temporal sequence of development of ARF from the use of antipsychotic medications in case reports.^{13,18,23} Notably, we observed attenuated risks of ARF within 15–90 days after discontinued therapy of antipsychotics, and the risk ceased when antipsychotic therapy was stopped for >90 days, all of which could not be revealed from the previous case-crossover study²⁴ due to the design nature. Similar to the previous case-crossover study of a COPD population,²⁴ we found that the adverse effect was dose-dependent, but more importantly, the present study showed that antipsychotic-associated ARF in current users was more sensitive to escalating dose levels than to increasing durations of therapy. In

TABLE 2 Association between risk of acute respiratory failure and use of antipsychotics stratified by time since most recent prescription^a

Antipsychotics use	Cases (n = 7084)		Controls (n = 12 785)		Crude OR	95% CI	P-value	Adjusted OR ^b	95% CI	P-value
	n	%	n	%						
Nonuse of antipsychotics	5250	74.1	10 624	83.1	Reference			Reference		
Current use ^c	691	9.8	516	4.0	2.71	2.41–3.05	<.001	2.33	2.06–2.64	<.001
New use	236	3.3	153	1.2	3.12	2.54–3.84	<.001	2.65	2.15–3.27	<.001
Prevalent use	455	6.4	363	2.8	2.54	2.20–2.92	<.001	2.19	1.89–2.53	<.001
Recent use ^c	167	2.4	158	1.2	2.14	1.72–2.67	<.001	1.79	1.43–2.25	<.001
New use	65	0.9	63	0.5	2.09	1.47–2.96	<.001	1.90	1.33–2.71	<.001
Prevalent use	102	1.4	95	0.7	2.17	1.64–2.88	<.001	1.71	1.28–2.28	<.001
Recent past use ^c	305	4.3	361	2.8	1.71	1.46–2.00	<.001	1.41	1.20–1.66	<.001
New use	125	1.8	145	1.1	1.74	1.37–2.22	<.001	1.40	1.09–1.79	.009
Prevalent use	180	2.5	216	1.7	1.69	1.38–2.06	<.001	1.41	1.15–1.73	.001
Past use ^c	305	4.3	494	3.9	1.25	1.08–1.45	.003	1.07	0.92–1.24	.41
Remote use ^c	366	5.2	632	4.9	1.17	1.03–1.34	.02	1.06	0.93–1.22	.37

Abbreviations: OR, odds ratio; CI, confidence interval.

^aRecency was defined from the end date of the most recent prescription up to the index date.

^bAdjusted for covariates that were measured during follow-up with standardized difference >0.1 between cases and controls as shown in Table 1.

^cCurrent, recent, recent past, past and remote use of antipsychotics was determined based on the gap of ≤14 days, 15–30 days, 31–90 days, 91–180 days and >180 days, respectively, from the end day of the most recent antipsychotics prescription to the index date.

addition, despite a small number of patients receiving a combination therapy of typical and atypical antipsychotics, we observed an approximately 5-fold increased risk of ARF from current use of both types of antipsychotics, which was approximately the sum of the individual risks of typical and atypical antipsychotics, indicating an additive effect of combination of both types on the respiratory failure outcome in general adults. On the contrary, this additive effect was not observed in COPD patients.²⁴ Additional large studies are needed to confirm the findings of the additive effect, and to understand why the effect was offset by the respiratory condition of COPD.

Our findings could be translated to several clinical implications. The observed risk of ARF with antipsychotics could occur in all adults who take antipsychotic medications, rather than confined to high-risk patients, such as COPD patients. According to our data, antipsychotic agents were largely used beyond the approved indications, which revealed the presence of potentially inappropriate use of these medications in the real world. Given that the observed respiratory adverse reaction from antipsychotics is severe and life-threatening, our findings highlight the unmet need to improve antipsychotic usage, and we strongly recommend clinicians to weigh in the risk of developing life-threatening ARF events when assessing the harms and benefits of antipsychotic therapy. Healthcare professionals also need to be vigilant for any symptoms of respiratory difficulties in patients currently receiving antipsychotic agents, regardless of the indications, dose and duration of the antipsychotic use. Particularly, although the majority of patients in our study received low-dose of antipsychotics for off-label use, our data revealed that use of the low-dose antipsychotics still needs to be closely monitored for occurrence of potential severe respiratory adverse events.

Acute dystonia from the blockage of **D₂ receptors** with antipsychotics could have underlined our observed phenomena since it could lead to lethal respiratory stridor due to laryngeal spasm.⁴¹ However, antipsychotic-induced acute dystonia rarely occurs in adults aged >45 years,⁴² and usually disappears after 96 hours of initiating an antipsychotic treatment.⁴³ This is in contrast to our findings. Our analysed subjects had a mean age of 61 years, and the observed ARF risk in the current study remained for recent and recent past users of antipsychotic agents, which probably precludes acute dystonia in larynx as the dominant factor for this adverse drug reaction. Antipsychotics may also act on **5-HT_{2A} receptor** in the medulla and could cause the collapse of upper respiratory muscles.^{24,44} Alternatively, antipsychotics could antagonize neurotransmitters **D₂**, **5-HT_{2A}** and **H₁ receptors** that activate the central respiratory pattern generator, and consequently interfere with genesis of respiratory rhythm and pattern.^{22,40} We suspect that the inhibition of the central respiratory system with use of antipsychotics is the most possible biological plausibility primarily because our findings on an increased risk of ARF from not only typical antipsychotics (primary **D₂** antagonism) but also atypical antipsychotics (primary **5-HT_{2A}** antagonism), as well as the observed additive effect from both types of antipsychotics all support this plausible mechanism.

There are several unique strengths in the current study. First, we analysed approximately 7000 cases of ARF and 12 000 matched controls from an adult population, a large sample size with sufficient statistical power and enhanced generalizability. Second, we balanced all covariates at baseline between cases and controls using a DRS-matched approach, and adjusted for the imbalanced factors preceding the index date, which could minimize the confounding effect. Third,

TABLE 3 Association between risk of acute respiratory failure and different utilizations of current use of antipsychotics

Antipsychotics use	Cases (n = 7084)		Controls (n = 12 785)		Crude OR	95% CI	P-value	Adjusted OR ^a	95% CI	P-value
	n	%	n	%						
Nonuse of antipsychotics	5250	74.1	10 624	83.1	Reference			Reference		
Current use of antipsychotics										
By class, n (%)										
Typical only	389	5.5	346	2.7	2.28	1.96–2.64	<.001	1.90	1.63–2.22	<.001
Atypical only	261	3.7	156	1.2	3.39	2.77–4.14	<.001	3.04	2.48–3.73	<.001
Both	41	0.6	14	0.1	5.93	3.23–10.88	<.001	4.95	2.67–9.18	<.001
By duration, n (%)										
1–14 days	357	5.0	288	2.3	2.51	2.14–2.94	<.001	2.10	1.79–2.48	<.001
15–30 days	68	1.0	59	0.5	2.33	1.64–3.31	<.001	1.99	1.39–2.84	<.001
31–90 days	106	1.5	56	0.4	3.83	2.77–5.30	<.001	3.22	2.31–4.49	<.001
>90 days	160	2.3	113	0.9	2.87	2.25–3.65	<.001	2.63	2.05–3.37	<.001
By dose										
≤0.25 DDD	471	6.7	417	3.3	2.29	2.00–2.62	<.001	1.96	1.70–2.25	<.001
0.26–0.5 DDD	86	1.2	55	0.4	3.16	2.25–4.45	<.001	2.78	1.97–3.93	<.001
0.51–1 DDD	91	1.3	33	0.3	5.58	3.74–8.32	<.001	4.87	3.24–7.31	<.001
>1 DDD	43	0.6	11	0.1	7.91	4.08–15.35	<.001	6.53	3.33–12.79	<.001
By route of administration										
Oral only	511	7.2	423	3.3	2.44	2.14–2.79	<.001	2.14	1.87–2.46	<.001
Any injection	180	2.5	93	0.7	3.92	3.04–5.04	<.001	3.13	2.41–4.05	<.001

Abbreviations: OR, odds ratio; CI, confidence interval; DDD, defined daily dose.

^aAdjusted for covariates that were measured during follow-up with standardized difference >0.1 between cases and controls as shown in Table 1.

TABLE 4 Association between risk of acute respiratory failure and different conditions of recent and recent past use of antipsychotic medications

Antipsychotics use	Cases (n = 7084)		Controls (n = 12 785)		Crude OR (95% CI)	Adjusted OR (95% CI) ^a
	n	%	n	%		
Nonuse of antipsychotics	5250	74.1	10 624	83.1	Reference	Reference
Use of antipsychotics						
By class						
Recent use^c						
Typical only	119	1.7	141	1.1	1.71 (1.34–2.18) ^b	1.43 (1.11–1.85) ^b
Atypical only	27	0.4	16	0.1	3.41 (1.84–6.34) ^b	2.74 (1.45–5.15) ^b
Both	NA	NA	NA	NA	NA	NA
Recent past use^c						
Typical only	251	3.5	326	2.6	1.56 (1.32–1.84) ^b	1.29 (1.08–1.53) ^b
Atypical only	38	0.5	32	0.3	2.40 (1.50–3.85) ^b	1.95 (1.20–3.15) ^b
Both	16	0.2	3	0.02	10.79 (3.14–37.05) ^b	7.87 (2.25–27.44) ^b
By duration						
Recent use^c						
1–14 days	89	1.3	115	0.9	1.57 (1.19–2.07) ^b	1.30 (0.98–1.74)
15–30 days	35	0.5	25	0.2	2.83 (1.69–4.74) ^b	2.39 (1.42–4.03) ^b
31–90 days	27	0.4	12	0.1	4.55 (2.30–8.99) ^b	3.91 (1.96–7.80) ^b
>90 days	16	0.2	6	0.1	5.40 (2.11–13.80) ^b	4.09 (1.58–10.64) ^b
Recent past use^c						
1–14 days	174	2.5	268	2.1	1.31 (1.08–1.59) ^b	1.10 (0.90–1.34)
15–30 days	57	0.8	55	0.4	2.10 (1.45–3.04) ^b	1.70 (1.16–2.49) ^b
31–90 days	54	0.8	25	0.2	4.37 (2.72–7.03) ^b	3.42 (2.11–5.54) ^b
>90 days	20	0.3	13	0.1	3.11 (1.55–6.26) ^b	2.36 (1.15–4.84) ^b
By dose						
Recent use^c						
≤0.25 DDD	123	1.7	131	1.0	1.90 (1.48–2.44) ^b	1.57 (1.22–2.02) ^b
0.26–0.5 DDD	19	0.4	12	0.1	3.20 (1.55–6.61) ^b	2.71 (1.30–5.65) ^b
>0.5 DDD ^d	25	0.5	14	0.1	3.61 (1.88–6.96) ^b	3.12 (1.61–6.07) ^b
Recent past use^c						
≤0.25 DDD	233	3.3	311	2.4	1.52 (1.28–1.80) ^b	1.26 (1.05–1.50) ^b
0.26–0.5 DDD	27	0.4	26	0.2	2.10 (1.23–3.60) ^b	1.73 (0.995–3.00)
>0.5 DDD ^d	45	0.6	24	0.2	3.79 (2.31–6.23) ^b	2.95 (1.78–4.90) ^b
By route of administration						
Recent use^c						
Oral only	93	1.3	101	0.8	1.86 (1.40–2.47) ^b	1.54 (1.16–2.06) ^b
Any injection	74	1.0	57	0.5	2.63 (1.86–3.72) ^b	2.21 (1.55–3.15) ^b
Recent past use^c						
Oral only	168	2.4	247	1.9	1.38 (1.13–1.68) ^b	1.19 (0.97–1.46)
Any injection	137	1.9	114	0.9	2.43 (1.89–3.12) ^b	1.85 (1.43–2.40) ^b

Abbreviations: OR, odds ratio; CI, confidence interval; DDD, defined daily dose; NA, not available.

^aAdjusted for covariates that were measured during follow-up with standardized difference >0.1 between cases and controls as shown in Table 1.^b $p < .05$.^cRecent and recent past use of antipsychotics was determined based on the gap of 15–30 days and 31–90 days, respectively, from the end day of the most recent antipsychotics prescription to the index date.^dWe combined the 0.51–1 DDD and >1 DDD strata of the recent and recent past use to 1 stratum (>0.51 DDD) due to <5 of cell size in the cases and controls.

FIGURE 2 Sensitivity analysis of ARF risk for current use of antipsychotics among a general adult population. ^a $P < .05$. ^b Major ARF risk factors including pneumonia, aspiration, pulmonary embolism, and pulmonary oedema which were measured before the index date. ^c Delirium patients were defined by having any delirium diagnosis, ICU visits or newly receiving benzodiazepine prescriptions in the 3 months before the index date. ^d Severe infection included acute bronchitis, human immunodeficiency virus/acquired immune deficiency syndrome, meningitis and tuberculosis measured in the 1 year prior to the index date. Abbreviations: COPD, chronic obstructive pulmonary disease; ARF, acute respiratory failure; ICU, intensive care unit; OR, odds ratio; CI, confidence interval

we pinpointed the specific utilizations of antipsychotics that could lead to the elevation of ARF risk. Fourth, measurement bias for antipsychotic use is minimal because antipsychotics are prescription drugs in our country, and we analysed a nationwide claims database that contained all antipsychotic prescriptions in outpatient, inpatient and emergency care settings.

Several limitations of the current study needed to be addressed. Despite our efforts for controlling covariates, selection bias was still possible due to several imbalanced characteristics preceding the index date between cases and controls. However, the observed risk from antipsychotics persisted after employing a case-crossover analysis and excluding important determinants of ARF such as pneumonia. Additionally, confounding by indication bias could not be ruled out; however, we reached similar findings after employing an active comparison with carbamazepine. Furthermore, we could have observed cardiogenic ARF from heart failure, whereas the observed risk of ARF did not vary by the presence or absence of the heart disease. Moreover, our findings might be subjected to protopathic bias, in which antipsychotics could be initiated for delirium as a prodrome of ARF. However, we persistently observed an increased risk of ARF with antipsychotic use after excluding the medical events related to delirium and disregarding use of antipsychotics in the 7 days preceding the index date. The validity of the employed diagnosis codes for identifying ARF events has not been ascertained; therefore, we identified the ARF events with an

accompanied procedure of intubation or ventilation. Also, our findings could have been influenced by unmeasured confounders, such as smoking status, alcohol consumption and obesity. Nevertheless, the observed risk of ARF remained significant when performing a self-matched case-crossover analysis, which enabled removal of time-invariant confounding, given only a 4-month period was employed with the case-crossover analysis, during which most of unmeasured confounders would not be expected to vary substantially. In addition, the rule-out analysis for evaluating the impact of an unmeasured confounder on our findings also indicated that this confounding was unlikely to occur. Finally, we could not directly quantify the excess mortality rate with antipsychotic use vs nonuse due to the study design and the adopted outcome of interest.

In conclusion, use of antipsychotic agents is associated with an increased risk of hospital or ER admission for ARF in general adults. Timing of antipsychotic use is determined to be a major effect modifier, with current use carrying the highest risk of >2-fold. The risk of ARF associated with current use of antipsychotics is found to be dose-dependent and markedly higher at doses of 1 DDD and above, but <10% of the adult population received this high dose of antipsychotics. We caution physicians to consider this severe respiratory risk, and to monitor any symptoms of respiratory difficulties in patients currently receiving antipsychotics, especially for those on high-dose antipsychotics.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Because this is a de-identified claims database-based study, this study was exempt from a full review of the Institutional Review Board of Tri-service General Hospital, National Defense Medical Center (B-104-16), and written informed consent was waived.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

Wang M.T., Lin C.W., Tsai C.L., Wang Y.H. and Hsu Y.J. contributed to conception and/or study design of this study; Wang M.T. acquired the analysed dataset; Wang Y.H. and Lai J.H. analysed the data; Lin C.W., Tsai C.L., Yeh C.B., Huang Y.L. and Hsu Y.J. gave administrative, technical or material supports; all authors interpreted the data; Wang M.T. and Lin C.W. drafted the manuscript; All authors made critical revisions of the manuscript and gave final approval of the submitted manuscript.

DATA AVAILABILITY STATEMENT

The availability of public access to the analysed database was restricted and forbidden by the current laws of Taiwan according to the regulations of the National Health Research Institutes (<http://nhird.nhri.org.tw>) and the Ministry of Health and Welfare (<https://dep.mohw.gov.tw/DOS/np-2497-113.html>). To request data access, it is suggested to contact the Health and Welfare Data Science Center, Ministry of Health and Welfare (<https://dep.mohw.gov.tw/DOS/np-2497-113.html>).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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