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Association Between Antipsychotic Agents and Risk of Acute Respiratory Failure in Patients With Chronic Obstructive Pulmonary Disease

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IMPORTANCE Acute respiratory failure (ARF) is a life-threatening event that has been linked in case reports to antipsychotic use, but this association lacks population-based evidence. Particular attention should be focused on patients with chronic obstructive pulmonary disease (COPD) regarding this drug safety concern because these patients are prone to ARF and are commonly treated with antipsychotics.

OBJECTIVE To determine whether the use of antipsychotics is associated with an increased risk of ARF in patients with COPD.

DESIGN, SETTING, AND PARTICIPANTS A population-based case-crossover study analyzing the Taiwan National Health Insurance Research Database was conducted of all patients with COPD, who were newly diagnosed with ARF in hospital or emergency care settings necessitating intubation or mechanical ventilation from January 1, 2000, to December 31, 2011. Patients with prior ARF, lung cancer, and cardiogenic, traumatic, or septic ARF were excluded to analyze idiopathic ARF. The pilot study was conducted from November 1 to December 31, 2013, and full data analysis was performed from October 15, 2015, to November 8, 2016.

EXPOSURES The use of antipsychotics was self-compared during days 1 to 14 (the risk period according to previous case reports) and days 75 to 88 (control period) preceding the ARF event or index date. The antipsychotic class, route of administration, and dose were also examined.

MAIN OUTCOMES AND MEASURES Risk of ARF.

RESULTS There were 5032 patients with ARF (mean [SD] age, 74.4 [9.9] years; 3533 males [70.2%]) among the 61 620 patients with COPD. Five hundred ninety patients with ARF (11.7%) filled at least 1 antipsychotic prescription during the case period compared with 443 (8.8%) during the control period, corresponding to a 1.66-fold (95% CI, 1.34-2.05; $P < .001$) adjusted increased risk of ARF regardless of antipsychotic class and administration route. A dose-dependent risk of ARF associated with antipsychotics was identified (test for trend, adjusted odds ratio, 1.35; 95% CI, 1.19-1.52; $P < .001$), which increased from a 1.52-fold risk for a low daily dose (95% CI, 1.20-1.92; $P < .001$) to a 3.74-fold risk for a high dose (95% CI, 1.68-8.36; $P = .001$). The increased risk persisted under a case-time-control analysis (adjusted odds ratio, 1.62; 95% CI, 1.16-2.27; $P = .005$) and nested case-control study (adjusted odds ratio, 2.16; 95% CI, 1.91-2.15; $P < .001$).

CONCLUSIONS AND RELEVANCE Antipsychotic use is associated with an acute and dose-dependent increased risk of ARF in patients with COPD. Clinicians should exercise caution when prescribing antipsychotics to patients with COPD and avoid high doses if possible.

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Supplemental content

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Chronic obstructive pulmonary disease (COPD) is a persistent inflammatory disease with irreversible airway limitation currently affecting 210 million people globally.[1,2] The disease is a leading cause of mortality worldwide[3] and is the eighth contributing factor to years lived with disability, which has increased by 72.3% from 1990 to 2013.[4] Acute respiratory failure (ARF) is a serious complication that frequently occurs in patients with COPD during acute exacerbation or is induced by a particular cause.[5] After an episode of ARF, 80% of patients with COPD are rehospitalized and require intensive care or mechanical ventilator support; 63% experience another severe respiratory outcome, and 49% die within 1 year.[6,7]

In recent decades, there have been reports of 12 patients expressing extreme difficulty breathing,[8-10] acute respiratory distress,[9-16] or ARF[8,16-18] requiring intubation or mechanical ventilation within hours and up to approximately 10 days after the use of antipsychotic drugs. Most of these patients took therapeutic doses of typical[9,10,13,14,16,17] or atypical[8,10,16-18] antipsychotics via either oral[8-10,13,16-18] or parenteral[10,14,17] routes of administration, while in 3 patients an overdose was identified.[11,12,15] Half of the patients concomitantly used medications that affect the central nervous system, such as benzodiazepines[8,14,16] and antidepressants.[8,11,15,16] As suggested, inhibition of serotonergic, dopaminergic, and histaminergic receptors by antipsychotics may cause improper respiratory muscle activity[9,10,12] or central respiratory depression.[8,14,17,18] Nonetheless, concern about the safety of antipsychotics in patients with COPD has not been examined via a population-based analysis.

Antipsychotics are frequently prescribed to patients with COPD despite the concerns regarding antipsychotic-associated ARF. Antipsychotics are primarily prescribed for schizophrenia, bipolar disorder, and other psychotic disorders and conditions,[19,20] but they are also increasingly used off-label to manage behavioral symptoms of dementia and insomnia.[20] Unnecessary treatment with antipsychotics in patients with COPD could be a major drug safety issue owing to a substantial proportion of patients using these medications for off-label indications.[21-23] Although the risks of metabolic disease[20] and sudden death[24] from treatment with antipsychotics have been explained, the respiratory effect of these drugs is not generally a clinical consideration for patients with COPD.

We therefore conducted a large observational study to quantify the association between use of antipsychotics and the risk of ARF in patients with COPD, excluding cardiogenic, traumatic, and septic conditions as the primary cause. We further examined whether the risk varies by antipsychotic class, daily dose, route of administration, individual agents, and receptor binding affinity of antipsychotics.

Key Points

Question Is the use of antipsychotic drugs associated with the risk of acute respiratory failure (ARF) in a population of patients with chronic obstructive pulmonary disease?

Findings In this population-based case-crossover study of 5032 patients with newly diagnosed ARF identified from 61 620 patients with chronic obstructive pulmonary disease, after accounting for cardiogenic, traumatic, and septic ARF as well as proxies of the severity of chronic obstructive pulmonary disease, the use of antipsychotic drugs was associated with a 1.66-fold increased risk of ARF within 14 days of therapy initiation.

Meaning These findings suggest an acute risk of ARF from antipsychotic use in patients with chronic obstructive pulmonary disease, and future studies are required to confirm the observed association.

Methods

Study Design

A case-crossover study design compared the use of antipsychotics during the period immediately before the ARF event (case period) and during an earlier control period for each patient with ARF. This within-self comparison design was a means by which to minimize interpersonal variation and control time-invariant covariates. Adoption of this design assumes transient exposure, no time trend in exposure, and an acute outcome. Antipsychotics are often used intermittently, and case reports have described acute onset of ARF following antipsychotic treatment.[8,16,17] The time trend assumption was examined in sensitivity analyses.

Data Source

We used the Taiwan Longitudinal Health Insurance Database (LHID) from January 1, 2000, to December 31, 2011, which is a subset of the National Health Insurance Research Database that covers 99% of the Taiwanese population enrolled in the compulsory and universal national health insurance program. During the same period, 2 sets of LHID data were analyzed, each containing 1 million randomly selected, mutually exclusive beneficiaries and including deidentified and encrypted information regarding medical diagnoses, procedures, and prescribed medications in inpatient, outpatient, and emergency care settings. The LHID has been widely used to study drug safety, including adverse respiratory events.[25] This study was exempt from a full review by the Tri-service General Hospital National Defense Medical Center Institutional Review Board.

Study Cohort

All patients with COPD documented in the LHID aged 40 years or older between January 1, 2001, and December 31, 2010, were identified. We adopted the previously reported criteria for identifying patients with COPD, which consisted of 2 COPD-associated outpatient visits within 1 year or 1 hospital visit for COPD (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 491, 492, and 496), accompanied by prescription records of medications for COPD.[26] The cohort entry date was the date of the patient's second outpatient visit or the hospital discharge date for COPD. To ensure that use of antipsychotics preceded the occurrence of ARF, we identified newly developed cases of ARF by excluding patients with a history of ARF and those with less than 1 full year of national health insurance enrollment in the year

before cohort entry. The follow-up period ended with the first occurrence of ARF, disenrollment from national health insurance, death, or the end of the study period (December 31, 2011). Death was determined from hospital claims data or derived from enrollment records showing permanent disenrollment from the compulsory national health insurance. The disenrollment information is required by law in Taiwan to be submitted within 3 days of death.[27,28]

Case Identification

Cases were incident hospitalization or emergency care for ARF (*ICD-9-CM* codes 518.81, 518.82, 518.84, or 786.09) in combination with intubation or mechanical ventilation. The date of admission for treatment of ARF served as the index date. Patients hospitalized across the case and control periods or those with a follow-up period less than 88 days were excluded owing to indeterminable prescription dates and incomplete medical records, respectively. Furthermore, we excluded patients with lung cancer during follow-up and those diagnosed with cardiogenic pulmonary edema, pulmonary insufficiency following trauma and surgery, sepsis, shock, or head or thoracic injury in the 88 days preceding and on the index date. eTable 1 in the Supplement details the operational definitions of cases.

Exposure to Antipsychotics

Use of antipsychotics was measured by examining records from outpatient, inpatient, and emergency care settings of prescriptions filled during the case and control periods, defined as 1 to 14 days and 75 to 88 days before the ARF events, respectively. The use of a 14-day period and a 60-day buffer period were set according to the previously mentioned case reports[8,16,17] and the half-lives of depot antipsychotics, respectively.

Use of antipsychotics was further assessed using multiple approaches. We classified antipsychotics into typical, atypical, and both types and measured the average daily dose of antipsychotics (≤0.25, 0.26-0.50, 0.51-1.00, or >1.00 defined daily dose). The route of antipsychotic administration (oral or any injection) and individual antipsychotics with sufficient sample sizes were also evaluated. In addition, antipsychotics were categorized into high and low affinities according to the median Ki value[29] (eTable 2 in the Supplement) for receptors found in the central respiratory network, including the dopamine D_2, dopamine D_1, serotonin $5HT_{2A}$, histamine-1, and muscarinic M_1 receptors.

We also measured the use of sennosides (common herbal laxatives) and opioids, which served as negative and positive controls, respectively. We anticipated no association between sennosides and ARF but did expect an increased adverse respiratory effect from excess opioids (≥1 defined daily dose).[30,31]

Measurement of Time-Variant Confounding Factors

Factors that could affect use of antipsychotics or cause ARF were measured separately in the 1 to 14 days (case period) and 75 to 88 days (control period) preceding the index date, including the following: (1) medications that depress the central nervous system, β-blockers, anticholinergics, lung-damaging agents, nonsteroidal anti-inflammatory drugs, antiplatelet agents, muscle relaxants, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and COPD medications; (2) COPD severity proxies (number of different COPD medications and number of emergency care or inpatient visits for COPD and number of COPD outpatient prescriptions for corticosteroids or antibiotics); and (3) patients' sex, age, and comorbidities (asthma, pneumonia, cardiovascular diseases, psychiatric diseases, gastroesophageal reflux disease, and cancer). We assessed the co-medications and comorbidities based on all records of prescriptions filled and any disease diagnoses in all medical care settings, respectively. Definitions of these covariates in patients with ARF are detailed in eTable 1 in the Supplement.

Statistical Analysis

The pilot study was conducted from November 1 to December 31, 2013, and full data analysis was performed from October 15, 2015, to November 8, 2016. The crude and adjusted odds ratios (ORs) of ARF associated with use of antipsychotics in the case period compared with the control period were calculated by conditional logistic regression. We adjusted for all time-varying factors with $P < .05$ considered significant (**Table 1**). Data-cleaning and statistical analyses were performed using SAS, version 9.2 (SAS Institute), and STATA, version 11 (STATA Corp), respectively. Multiple sensitivity analyses were conducted (eBox in the Supplement), such as performing a case-time-control study (eAppendix and eFigure 1 in the Supplement), a nested case-control study (eAppendix in the Supplement), adopting a lag-time approach to address protopathic bias (eAppendix and eFigure 2 in the Supplement), varying lengths of case and control periods in the case-crossover design (eFigure 3 in the Supplement), and adopting the rule-out approach for unmeasured confounding (eFigure 4 in the Supplement). Numbers needed to harm for the observed significant associations were estimated based on a published formula.[32]

Results

We identified 11 785 incident cases of ARF in 61 620 patients with COPD during a mean (SD) of 3.5 (2.8) years, which corresponded to an incidence rate of 3.5 per 100 person-years. After applying the exclusion criteria, 5032 incident cases of ARF were analyzed (eFigure 5 in the Supplement). Most patients with ARF were male (3533 [70.2%]), with a mean (SD) age of 74.4 (9.9) years; the demographic and clinical characteristics of all patients with ARF and their comparisons with controls in the adopted nested case-control study design are shown in eTable 3 and eTable 4 in the Supplement, respectively. Table 1 presents a comparison of the characteristics between the case and control periods among all patients with ARF. More than half of the measured characteristics were balanced between the 2 periods; however, it was more common in the case period than the control period for patients with ARF to have an acute severe exacerbation of COPD (917 [18.2%] vs 627 [12.5%]; $P < .001$), have experienced at least 1 admission to the intensive care unit

Table 1. Clinical Characteristics Between the Case Period and Matched Control Period in Patients With ARF[a]

Characteristic	No. (%)		Crude Odds Ratio (95% CI)	*P* Value[b]
	Case Period (n = 5032)	Control Period (n = 5032)		
Admission to intensive care unit	134 (2.7)	95 (1.9)	1.45 (1.10-1.91)	.008
Comorbidities				
Cardiovascular disease				
Stroke	980 (19.5)	955 (19.0)	1.10 (0.93-1.30)	.29
Ischemic heart disease	792 (15.7)	771 (15.3)	1.10 (0.91-1.32)	.32
Heart faliure	566 (11.3)	490 (9.7)	1.46 (1.20-1.78)	<.001
Arrhythmia	40 (0.8)	44 (0.9)	0.81 (0.43-1.53)	.52
Pulmonary disease				
Pneumonia	550 (10.9)	392 (7.8)	1.57 (1.35-1.83)	<.001
Asthma	782 (15.5)	676 (13.4)	1.46 (1.24-1.73)	<.001
Psychiatric disease				
Dementia	466 (9.3)	473 (9.4)	0.95 (0.75-1.20)	.68
Anxiety	255 (5.1)	259 (5.2)	0.96 (0.72-1.28)	.77
Depression	146 (2.9)	145 (2.9)	1.02 (0.67-1.57)	.91
Bipolar disorder	89 (1.8)	89 (1.8)	1.00 (0.55-1.81)	>.99
Schizophrenic disorder	28 (0.6)	31 (0.6)	0.40 (0.08-2.06)	.27
Delirium	20 (0.4)	20 (0.4)	1.00 (0.43-2.31)	>.99
Cancer, except for lung cancer	388 (7.7)	341 (6.8)	1.55 (1.18-2.04)	.002
Gastroesophageal reflux disease	115 (2.3)	97 (1.9)	1.43 (0.96-2.12)	.08
Medication use				
Cardiovascular drugs				
Antiplatelet agents	1506 (29.9)	1490 (29.6)	1.05 (0.90-1.23)	.53
Angiotensin II receptor blockers	715 (14.2)	748 (14.9)	0.82 (0.66-1.02)	.70
Angiotensin-converting enzyme inhibitors	524 (10.4)	512 (10.2)	1.07 (0.87-1.33)	.51
β-Blockers				
Cardiovascular selective	302 (6.0)	308 (6.1)	0.93 (0.69-1.26)	.64
Noncardiovascular selective	425 (8.5)	372 (7.4)	1.38 (1.11-1.72)	.004
Statins	222 (4.4)	239 (4.8)	0.78 (0.55-1.09)	.15
CNS depressive drugs				
Antihistamines				
First generation	1289 (25.6)	1066 (21.2)	1.42 (1.27-1.59)	<.001
Second and third generation	542 (10.8)	497 (9.9)	1.15 (0.98-1.35)	.07
Antidepressants				
SSRIs and SNRIs	117 (2.3)	123 (2.4)	0.87 (0.57-1.33)	.52
TCAs	164 (3.3)	151 (3.0)	1.19 (0.86-1.65)	.28
Other antidepressants	150 (3.0)	146 (2.9)	1.10 (0.72-1.66)	.67
BZDs and non-BZDs	1756 (34.9)	1588 (31.6)	1.40 (1.23-1.58)	<.001
Antidopaminergic agents	1189 (23.6)	960 (19.1)	1.56 (1.38-1.77)	<.001
Opioids	398 (7.9)	241 (4.8)	2.15 (1.76-2.64)	<.001
Anesthetics	78 (1.6)	52 (1.0)	1.70 (1.13-2.56)	.01
Barbiturates	49 (1.0)	43 (0.9)	1.21 (0.74-2.00)	.45
Anticholinergic agents				
Gastrointestinal antispasmodics	201 (4.0)	157 (3.1)	1.41 (1.10-1.80)	.007
Bladder antimuscarinics	94 (1.9)	112 (2.2)	0.70 (0.48-1.04)	.08
Antiparkinsonian agents	125 (2.5)	117 (2.3)	1.36 (0.79-2.36)	.27
Nonsteroidal anti-inflammatory drugs	1602 (31.8)	1283 (25.5)	1.62 (1.45-1.81)	<.001
Muscle relaxants	402 (8.0)	373 (7.4)	1.13 (0.94-1.35)	.19
Respiratory failure–causing drugs	494 (9.8)	435 (8.6)	1.38 (1.12-1.70)	.002
Amiodarone hydrochloride	176 (3.5)	143 (2.8)	1.94 (1.29-2.92)	.001

(continued)

Table 1. Clinical Characteristics Between the Case Period and Matched Control Period in Patients With ARF[a] (continued)

Characteristic	No. (%)		Crude Odds Ratio (95% CI)	P Value[b]
	Case Period (n = 5032)	Control Period (n = 5032)		
COPD medications				
SABAs				
Nebulized	213 (4.2)	111 (2.2)	2.42 (1.84-3.18)	<.001
Inhaled	1374 (27.3)	965 (19.2)	2.22 (1.96-2.53)	<.001
SAMAs				
Nebulized	787 (15.6)	405 (8.1)	2.64 (2.27-3.07)	<.001
Inhaled	585 (11.6)	434 (8.6)	1.89 (1.57-2.27)	<.001
Inhaled cortiocosteroids	569 (11.3)	559 (11.1)	1.05 (0.87-1.27)	.62
LABAs	471 (9.4)	446 (8.9)	1.18 (0.94-1.48)	.15
LAMAs	178 (3.5)	182 (3.6)	0.93 (0.65-1.34)	.71
Methylxanthines	1475 (29.3)	1405 (27.9)	1.19 (1.03-1.36)	.02
Proxy indicators for COPD severity				
Type of COPD medications, No.				
0	2720 (54.1)	2996 (59.5)	1 [Reference]	
1-2	1446 (28.7)	1331 (26.5)	1.52 (1.34-1.73)	<.001
≥3	866 (17.2)	705 (14.0)	2.12 (1.78-2.53)	<.001
Emergency department visits or hospitalizations for COPD, No.				
0	4005 (79.6)	4306 (85.6)	1 [Reference]	
1	917 (18.2)	627 (12.5)	1.64 (1.46-1.84)	<.001
≥2	110 (2.2)	99 (2.0)	1.31 (0.98-1.75)	.06
Oral corticosteroids or antibiotics prescribed at COPD outpatient visits, No.				
0	4702 (93.4)	4793 (95.3)	1 [Reference]	
1	246 (4.9)	162 (3.2)	1.78 (1.41-2.25)	<.001
≥2	84 (1.7)	77 (1.5)	1.35 (0.94-1.93)	.10

Abbreviations: ARF, acute respiratory failure; BZD, benzodiazepine; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; LABAs, long-acting β_2 agonists; LAMAs, long-acting muscarinic antagonists; SABAs, short-acting β_2 agonists; SAMAs, short-acting muscarinic antagonists; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

[a] Each confounder was measured during the case and control periods.

[b] *P* value was obtained by conditional logistic regression.

Table 2. Risk of Acute Respiratory Failure Associated With Any Use of Antipsychotics, Positive Control and Negative Control

Characteristic	No. (%)		Crude Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio[a] (95% CI)	P Value
	Case Period (n = 5032)	Control Period (n = 5032)				
No use of antipsychotics	4442 (88.3)	4589 (91.2)	1 [Reference]		1 [Reference]	
Any use of antipsychotics	590 (11.7)	443 (8.8)	2.05 (1.67-2.51)	<.001	1.66 (1.34-2.05)	<.001
Opioid[b]	85 (1.7)	45 (0.9)	2.43 (1.56-3.77)	<.001	2.00 (1.26-3.20)	.004
Sennoside	1568 (31.2)	1448 (28.8)	1.29 (1.14-1.47)	<.001	1.05 (0.91-1.21)	.54

[a] Adjusted for admission to intensive care unit, heart failure, pneumonia, asthma, cancer, antiplatelet agents, angiotensin-converting enzyme inhibitors, noncardiovascular-selective β-blockers, first-generation antihistamines, benzodiazepines and nonbenzodiazepines, antidopaminergic agents, opioids, anesthetics, gastrointestinal antispasmodics, anticholinergic agents, nonsteroidal anti-inflammatory drugs, respiratory failure–causing drugs, amiodarone hydrochloride, nebulized and inhaled short-acting β_2 agonists, nebulized and inhaled short-acting muscarinic antagonists, methylxanthines, types of medications for chronic obstructive pulmonary disease, number of emergency department visits or hospitalizations for chronic obstructive pulmonary disease, and number of corticosteroids or antibiotics prescribed at outpatient visits.

[b] Restricted to >1 defined daily dose, and the adjusted odds ratio did not include the drug itself.

(134 [2.7%] vs 95 [1.9%]; *P* = .008), have a diagnosis of pneumonia (550 [10.9%] vs 392 [7.8%]; *P* < .001) or cancer (388 [7.7%] vs 341 [6.8%]; *P* = .002), and have records of filling prescriptions for benzodiazepine and nonbenzodiazepine insomnia medications (1756 [34.9%] vs 1588 [31.6%]; *P* < .001), opioids (398 [7.9%] vs 241 [4.8%]; *P* < .001), and inhaled short-acting β_2 agonists (1374 [27.3%] vs 965 [19.2%]; *P* < .001) and inhaled short-acting muscarinic antagonists (585 [11.6%] vs 434 [8.6%]; *P* < .001), although most of the differences between the periods were less than 5%.

Table 2 indicates that 590 patients (11.7%) filled at least 1 prescription for an antipsychotic medication during the case period compared with 443 patients (8.8%) during the control period, corresponding to a crude OR of 2.05 (95% CI, 1.67-2.51) and adjusted OR (AOR) of 1.66 (95% CI, 1.34-2.05). The full multivariate model is shown in eTable 5 in the Supple-

Table 3. Risk of Acute Respiratory Failure Associated With Different Conditions of Antipsychotic Use

Characteristic	No. (%) Case Period (n = 5032)	Control Period (n = 5032)	Crude Odds Ratio (95% CI)	*P* Value	Adjusted Odds Ratio (95% CI)[a]	*P* Value
No use of antipsychotics	4442 (88.3)	4589 (91.2)	1 [Reference]		1 [Reference]	
Any use of antipsychotics						
Antipsychotic class						
Typical only	310 (6.2)	202 (4.0)	2.17 (1.70-2.76)	<.001	1.70 (1.31-2.19)	<.001
Atypical only	238 (4.7)	215 (4.3)	1.68 (1.17-2.40)	.005	1.53 (1.05-2.22)	.03
Both	42 (0.8)	26 (0.5)	2.73 (1.46-5.10)	.002	1.96 (1.02-3.80)	.05
Route of administration						
Oral only	479 (9.5)	387 (7.7)	1.92 (1.52-2.41)	<.001	1.72 (1.35-2.19)	<.001
Any injection	111 (2.2)	56 (1.1)	2.43 (1.71-3.46)	<.001	1.48 (1.01-2.17)	.04
Dose						
Low (≤0.25 DDD)	383 (7.6)	299 (5.9)	1.86 (1.49-2.32)	<.001	1.52 (1.20-1.92)	<.001
Medium (0.26-0.50 DDD)	84 (1.7)	65 (1.3)	2.33 (1.49-3.63)	<.001	2.10 (1.32-3.32)	.002
Medium high (0.51-1.00 DDD)	80 (1.6)	56 (1.1)	2.51 (1.58-3.98)	<.001	1.76 (1.08-2.89)	.02
High (>1.00 DDD)	43 (0.9)	23 (0.5)	4.72 (2.19-10.20)	<.001	3.74 (1.68-8.36)	.001
By affinity[b]						
Serotonin $5HT_{2A}$ receptor						
Low affinity	335 (6.7)	281 (5.6)	1.71 (1.32-2.22)	<.001	1.41 (1.07-1.86)	.02
High affinity	255 (5.1)	147 (2.9)	2.89 (2.15-3.88)	<.001	2.28 (1.67-3.10)	<.001
Dopamine D_2 receptor						
Low affinity	359 (7.1)	303 (6.0)	1.70 (1.31-2.19)	<.001	1.38 (1.05-1.81)	.02
High affinity	231 (4.6)	125 (2.5)	3.05 (2.24-4.14)	<.001	2.45 (1.77-3.38)	<.001
Histamine-1 receptor						
Low affinity	237 (4.7)	174 (3.5)	2.17 (1.58-2.97)	<.001	1.87 (1.35-2.60)	<.001
High affinity	353 (7.0)	254 (5.1)	2.18 (1.69-2.80)	<.001	1.69 (1.29-2.20)	<.001
Dopamine D_1 receptor						
Low affinity	395 (7.9)	307 (6.1)	2.17 (1.66-2.83)	<.001	1.83 (1.39-2.42)	<.001
High affinity	83 (1.7)	68 (1.4)	1.85 (1.10-3.10)	.02	1.49 (0.87-2.56)	.15
Muscarinic M_1 receptor						
Low affinity	172 (3.4)	122 (2.4)	2.61 (1.79-3.82)	<.001	2.21 (1.47-3.30)	<.001
High affinity	206 (4.1)	172 (3.4)	2.01 (1.39-2.93)	<.001	1.53 (1.03-2.27)	.04

Abbreviation: DDD, defined daily dose.

[a] Adjusted for admission to intensive care unit, heart failure, pneumonia, asthma, cancer, antiplatelet agents, angiotensin-converting enzyme inhibitors, noncardiovascular-selective β-blockers, first-generation antihistamines, benzodiazepines and nonbenzodiazepines, antidopaminergic agents, opioids, anesthetics, gastrointestinal antispasmodics, anticholinergic agents, nonsteroidal anti-inflammatory drugs, respiratory failure–causing drugs, amiodarone hydrochloride, nebulized and inhaled short-acting β_2 agonists, nebulized and inhaled short-acting muscarinic antagonists, methylxanthines, types of medications for chronic obstructive pulmonary disease, number of emergency department visits or hospitalizations for chronic obstructive pulmonary disease, and number of corticosteroids or antibiotics prescribed at outpatient visits.

[b] Only the antipsychotics with Ki values were analyzed.

ment. A significant and a null association was found with use of positive (AOR, 2.00; 95% CI, 1.26-3.20; *P* = .004) and negative control agents (AOR, 1.05; 95% CI, 0.91-1.21; *P* = .54), respectively, as expected.

Significantly increased risks of ARF with the use of typical (AOR, 1.70; 95% CI, 1.31-2.19) and atypical antipsychotics (AOR, 1.53; 95% CI, 1.05-2.22) were identified (**Table 3**). The AOR for administration via injection was 1.48 (95% CI, 1.01-2.17), and the AOR for oral administration was 1.72 (95% CI, 1.35-2.19). A linear dose-dependent association (test for trend, AOR, 1.35; 95% CI, 1.19-1.52; *P* < .001) was identified, with the risk increasing from 1.52-fold to 3.74-fold as the daily dose of antipsychotics increased from low to high. The differences in the risk of ARF between low- and high-affinity antipsychotics were significantly greater for serotonin $5HT_{2A}$ and dopamine D_2 receptors than for other receptors, as identified in head-to-head analyses with dose adjustment (eTable 6 in the Supplement). Individual drug analyses revealed that the use of prochlorperazine maleate and prochlorperazine methanesulfonate, haloperidol decanoate, sulpiride, quetiapine fumarate, or risperidone was associated with a significantly increased risk of ARF ranging from 1.80-fold to 2.34-fold (eTable 7 in the Supplement).

Our main findings were robust in most of the sensitivity analyses. The results were replicated in case-time-control (adjusted odds ratio, 1.62; 95% CI, 1.16-2.27; *P* = .005) and nested case-control studies (adjusted odds ratio, 2.16; 95% CI, 1.91-2.15; *P* < .001) (eTable 8 and eFigure 6 in the Supplement), persisted across various case and control periods, and remained with use of a 7-day and 14-day lag-time period immediately

preceding the observed ARF outcome (eFigure 6 in the Supplement). The findings remained significant after excluding patients with delirium or heart failure and those who used nebulized short-acting β_2 agonists or short-acting muscarinic antagonists. The risk of ARF did not vary across all subgroup analyses, including severity of COPD (AOR of the interaction term, 0.74; 95% CI, 0.42-1.30; $P = .29$) and asthma comorbidity (AOR, 1.06; 95% CI, 0.70-1.60; $P = .78$). eFigure 4 in the Supplement indicates that an unmeasured confounder needs to increase the risk of ARF risk by 6-fold and to be 9.63 times more prevalent in antipsychotic users than nonusers to fully explain our findings.

eTable 9 in the Supplement presents the data on the number needed to harm, showing that 347 (95% CI, 218-673) patients needed to receive any antipsychotics to cause an additional ARF event. The number needed to harm was only 87 (95% CI, 31-337) for high-dose antipsychotics.

Discussion

Our case-crossover study of 5032 incident cases of ARF identified from 61 620 patients with COPD revealed an overall 66% increase in the risk of ARF during the first 2 weeks of antipsychotic use, independent of cardiogenic, traumatic, and septic factors. The association of the risk of ARF with use of antipsychotics was dose dependent; the risk occurred with a dose of antipsychotics as low as 0.25 defined daily dose or less, and increased by more than 3-fold with a daily dose of 1 defined daily dose or more. The observed risk persisted under 3 different study designs, and protopathic bias was addressed using the lag-time approach.

The results of this study indicated a life-threatening adverse respiratory effect of antipsychotic treatment, which has been described previously only in case reports.[8-18] Patients taking haloperidol,[9,10,13,17] chlorpromazine,[10] pericyazine,[16] droperidol,[14] olanzapine,[10,16,18] quetiapine,[8,15,17] or risperidone[8,10-12] have been reported to have developed ARF, with signs of hypoxia,[8,9,12-17] coma,[8,10,12,15,17,18] laryngeal dystonia,[9,10] and respiratory depression and distress.[8,12,17,18] These ARF events occurred without any cardiac[9,12,15-17] or neurologic[8,9,12,13,17] events, allergic responses,[9,10] or other respiratory abnormalities.[8-10,14] Moreover, cases of ARF have been detected shortly after increasing the dose[9,18] or overdose[11,12,15] of antipsychotics, while cessation of antipsychotics led to resolution of symptoms within 48 hours.[8,18] Nevertheless, the causality of these case reports could not be established primarily owing to danger of confounding, overinterpretation, and publication bias.

Our population-based study not only adds to the current limited safety evidence but also pinpoints specific antipsychotics and doses that should be prescribed with caution. We recommend that health care professionals be vigilant regarding signs of ARF among patients with COPD who are receiving antipsychotics, especially during the initial treatment phase. Switching the type of antipsychotic may not mitigate the risk of ARF, as typical and atypical antipsychotics were found to have similar risks. Reducing the dose of antipsychotics seems to be a plausible strategy for lowering the risk of ARF but does not completely eradicate it, while high doses of antipsychotics should always be avoided whenever possible.

There are several plausible pathways underlying antipsychotic-induced ARF, although the exact mechanisms are unclear. First, ex vivo evidence has shown that agonists for serotonin $5HT_{2A}$,[33] dopamine D_1,[34] and histamine-1 receptors[35] activate the respiratory pattern generator in the brainstem, which is an effect that could be inhibited by antipsychotics. Second, blockage of dopamine D_2 receptors could induce dystonia in the larynx,[9] potentially causing stridor and difficulty breathing. Third, loss of serotonin $5HT_{2A}$ activity in the medulla could lead to collapse of upper airway muscles,[36] presenting as another potential adverse respiratory outcome following treatment with serotonin $5HT_{2A}$ receptor–inhibiting antipsychotics. Our affinity results supported all 3 biological mechanisms, but indicated antipsychotics were more likely to act via dopamine D_2 and serotonin $5HT_{2A}$ receptors to induce ARF. We also identified a comparable risk of ARF between atypical and typical antipsychotics (AOR, 0.84; 95% CI, 0.54-1.30), which have unique receptor binding profiles, evidence that supports both the dopaminergic and serotonergic pathways.

The observed association between use of antipsychotics and risk of ARF is probably not mediated through pneumonia nor confined to patients with severe COPD. Although antipsychotics have been linked to pneumonia,[37] the observed increased risk of ARF persisted following exclusion of any ARF events accompanied by a diagnosis of pneumonia and adjustment for earlier pneumonia events. This finding ruled out the possibility of pneumonia acting as an intermediator in the observed association. Owing to a lack of data regarding lung functions, we could not determine whether antipsychotics directly cause ARF or indirectly exacerbate COPD. Nevertheless, we observed a persistent, significantly increased risk of ARF when restricting patients to those with no prior COPD exacerbation or excluding those with immediate prior use of nebulized short-acting β_2 agonists and short-acting muscarinic antagonists, which implied a minimal effect of COPD severity and acute exacerbation.

Several alternative explanations may account for our findings, the plausibilities of which were assessed. First, the major concern was protopathic bias, in which a prodrome of ARF could have promoted use of antipsychotics. We observed a persistent significant association after excluding a 7-day and 14-day period preceding the ARF diagnosis when measuring use of antipsychotics to not capture any use of antipsychotics intended for ARF prodromal symptoms. Second, despite the adoption of a case-only design with strict exclusion criteria, many characteristics differed between the 2 periods, which suggested additional confounding, although many of the characteristics were associated with worsening of respiratory function preceding diagnosis of ARF. Nonetheless, our rule-out analysis indicated that unmeasured confounding was unlikely to have fully explained our findings. Third, the presence of severe mental illness could have confounded the dose effect. Nevertheless, exclusion of patients with schizophrenia or bipolar disorder did not change the dose-dependent effect (test for trend, AOR, 1.42; 95% CI, 1.24-1.63; $P < .001$).

Several unique attributes of our study warrant mentioning. This was the first population-based observational study to identify an increased risk of ARF associated with use of antipsychotics among patients with COPD. We analyzed incident idiopathic ARF events with other causes precluded, used a case-only design to control time-invariant confounding and avoid selection bias, and performed negative and positive control analyses for verifying specificity of the association. In addition, we observed an apparent dose response and replicated the findings with different study designs. Furthermore, we considered a wide range of acute confounding conditions that could differ within individuals.

Limitations

Our findings should be interpreted within the context of the study's limitations. First, confounding by indication bias was possible since psychosis can worsen patients' lung functions.[38] Nevertheless, baseline psychosis was comparable in the case and control periods, and the risk was unchanged with exclusion of patients with delirium. Arguably, antipsychotics are increasingly prescribed for vomiting and nausea, but vomiting rarely advances to aspiration despite the link between aspiration and ARF.[39,40] Second, the accuracy of the adopted *ICD-9-CM* codes for ARF was not ascertained; however, we restricted cases of ARF to patients who underwent intubation or mechanical ventilation. Third, several important confounders, such as lung function test results and smoking status, were unavailable in the LHID database, and time-varying unmeasured confounding could not be ruled out. Nevertheless, conditions in which an unmeasured confounder would fully explain our findings were unlikely to have occurred based on rule-out analysis. Fourth, the results for individual antipsychotics might be of insufficient statistical power. Fifth, adherence to antipsychotic treatment was unable to be assessed; however, this effect should not differ between the case and control periods, potentially leading to underestimation of the risk.

Conclusions

We identified a dose-dependent increased risk of ARF associated with use of antipsychotics in a population of patients with COPD, which rapidly occurred within 2 weeks of initiation of antipsychotic therapy. Further studies are needed to confirm the observed association. Meanwhile, we recommend that health care professionals weigh this risk against the beneficial effects of antipsychotic treatment in patients with COPD.

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