Antipsychotic Use and Bloodstream Infections Among Adult Patients With Chronic Obstructive Pulmonary Disease: A Cohort Study

Augusto Ferraris, MD[a,b]; Belén Blasco, MD[c]; Nicolás Tentoni, MD[a,b]; Facundo Del Olmo, MD[a]; Tomás Barrera, MD[b]; Federico Angriman, MD, MPH[d,e]; and Alejandro G. Szmulewicz, MD, MPH[f,*]

ABSTRACT

Objective: Mounting evidence suggests that antipsychotics may have immunomodulatory effects, but their impact on disseminated infections remains unknown. This study thus sought to estimate the effect of antipsychotic treatment on the occurrence of bloodstream infection during long-term follow-up in adult patients with chronic obstructive pulmonary disease.

Methods: This retrospective cohort study, with new user and active comparator design, included adult patients seen from January 2008 to June 2018 in a tertiary teaching hospital in Buenos Aires, Argentina. New users of antipsychotic drugs were compared to new users of any benzodiazepine. The primary outcome of interest was incident bloodstream infection at 1 year of follow-up. Propensity score methods and a Cox proportional hazards model were used to adjust for baseline confounding.

Results: A total of 923 patients were included in the present analysis. Mean (SD) age was 75.0 (9.8) years, and 51.9% of patients were female. The cumulative incidence of bloodstream infections at 1 year was 6.0% and 2.3% in the antipsychotic and benzodiazepine groups, respectively. Antipsychotic use was associated with a higher risk of bloodstream infections during the first year of follow-up (hazard ratio [HR] = 2.41; 95% CI, 1.13 to 5.14) compared to benzodiazepine use. Antipsychotics with high dopamine receptor affinity presented greater risk than less selective agents (HR = 5.20; 95% CI, 1.53 to 17.67).

Conclusions: Antipsychotic use is associated with bloodstream infections during the first year of follow-up in adult patients with chronic obstructive pulmonary disease. Further studies are warranted to confirm our findings and evaluate this effect in a broader population of patients.

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[a]Department of Internal Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[b]Pharmacology Department, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina

[c]Hospital de Emergencias Psiquiátricas Torcuato de Alvear, Buenos Aires, Argentina

[d]Institute for Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

[e]Department of Critical Care Medicine. Sunnybrook Health Sciences Centre, Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada

[f]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

**Corresponding author:* Alejandro G. Szmulewicz, MD, MPH, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Ave, Boston, MA, 02115 (als1284@g.harvard.edu).

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide,[1,2] and its prevalence among patients with severe mental illnesses is as high as 20%.[3] Mental disorders contribute to a substantial burden of COPD-related morbidity and may affect both quality of life and treatment adherence.[4]

The use of antipsychotics has been associated with life-threatening adverse events including stroke, hip fracture, venous thromboembolism, cardiac arrhythmias, acute respiratory failure, and coronary heart disease in patients with dementia, schizophrenia, drug abuse, anxiety, and bipolar disorders, among other conditions.[5–7] Furthermore, antipsychotics may increase the risk of both urinary tract infections and pneumonia[8,9] by mechanisms that likely include modulation of the immune response.[10] Specifically, data on the immunomodulatory effect of antipsychotic agents derived from clinical studies and in vitro models revealed decreased circulating levels of γ-interferon and interleukin (IL)-1, IL-2, and IL-6 and an increase in the circulating levels of IL-10 and transforming growth factor β.[11,12] Finally, antipsychotic drugs may also reduce the in vitro phagocytic and oxidative capacity of macrophages.[13] Therefore, the immunologic response may be impaired among antipsychotic drug users, increasing the risk of severe bacterial infections. However, the effect of antipsychotic treatment on the occurrence of disseminated infections in general—and bloodstream infections in particular—remains unknown.

Given that more than 10% of COPD patients fill at least one prescription for an antipsychotic agent over a follow-up period of 1 year,[14] and that COPD patients in general are at a higher risk of systemic infections and their complications,[15] there is an ongoing need to further characterize this practice.[16] We thus conducted a retrospective cohort study of adult patients with COPD to evaluate the effect of antipsychotic drug use on incident bloodstream infections.

METHODS

Data Source and Study Population

The present retrospective cohort study of adult patients with COPD from a tertiary teaching hospital

Clinical Points

- Mounting evidence suggests that antipsychotics may have immunomodulatory effects that could increase the risk of disseminated infections.
- Among patients with chronic obstructive pulmonary disease, the present study suggests that new antipsychotic drug use may be associated with a 2-fold increase in the risk of bloodstream infections during follow-up.
- Antipsychotics with high dopamine D_2 receptor affinity may present with higher risk of bloodstream infections than antipsychotics with low affinity.

in Buenos Aires, Argentina, was conducted using data for patients seen from January 2008 to June 2018. Patients aged 40 years or older were included if they had a COPD diagnosis and at least one prescription for inhaled bronchodilators or corticosteroids noted in the administrative database. Data were retrieved from electronic medical charts in which comprehensive information on demographic, clinical, pharmacologic, and laboratory data with long term follow-up is collected. Clinical diagnoses are coded in health records using SNOMED CT,[17] and all drug dispensing events are documented in the pharmacy's registry using the Anatomical Therapeutic Chemical (ATC) code. The authors asserted that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Our study protocol was approved by our local ethics review board (protocol number 1002). This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[18]

Exposure

The exposure of interest was incident prescription of any antipsychotic drug (ie, no prior antipsychotics dispensed in the last 60 days before the COPD diagnosis). We captured both the oral and depot intramuscular formulations of the locally available antipsychotics dispensed in the ambulatory setting using the ATC code and estimated defined daily doses (low, medium, medium-high, and high doses as described by Wang et al[14]). The reference group comprised incident users of benzodiazepines (ie, no prior benzodiazepine drugs dispensed in the last 60 days before the COPD diagnosis).

We defined index date as the date of incident antipsychotic drug prescription. For patients who did not receive an antipsychotic prescription during follow-up, index date was defined as the date of incident benzodiazepine drug prescription. Since our target population comprised mainly older adults, we considered, a priori, main reasons for antipsychotic prescription to be the treatment of delirium, psychiatric symptoms in the context of dementia, or insomnia/anxiety symptoms that are frequent in older adults. Given that the two most frequent treatment choices for these conditions are antipsychotics and benzodiazepines,[19,20] we chose the latter to serve as our reference group.

Outcome

The primary outcome was incident bloodstream infection during 1 year of follow-up. Bloodstream infection was defined as a positive blood culture for a non-contaminant pathogen isolated after at least 7 days of drug exposure. Source of infection was assessed by two investigators (F.D.O. and T.B.) by manually reviewing electronic medical charts.

Additional Covariates of Interest

Information regarding age, sex, and comorbidities (cardiac failure, coronary heart disease, stroke, diabetes, hypertension, chronic kidney disease, active malignancy, smoking status, dementia, and anxiety and depressive disorders) was captured at the time of COPD diagnosis from electronic medical charts. We performed random auditing of data and modified the search criteria employed to identify patient's comorbidities coded with SNOMED CT in the electronic medical charts until they had a coincidence of over 95% with the patient's clinical diagnosis.

Statistical Analysis

Clinical, pharmacologic, and demographic characteristics of patients are described using proportions, mean and standard deviation (SD), or median and interquartile range (IQR) as appropriate. We ascertained between-group differences (between antipsychotic and benzodiazepine groups) at baseline using standardized mean differences.

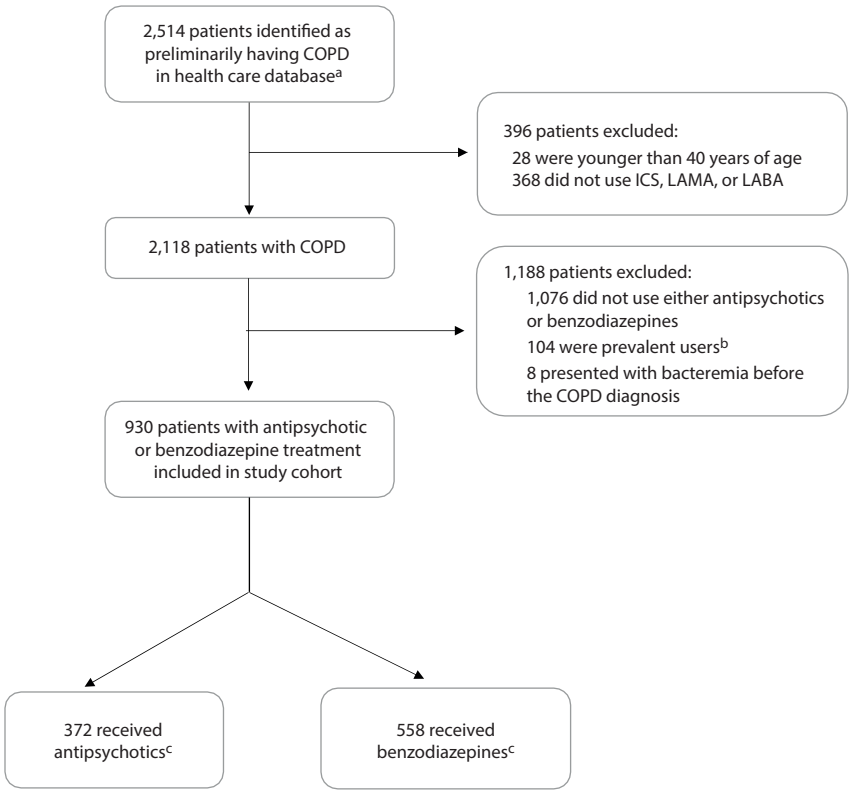
Patients were followed from index date until the occurrence of the primary outcome, all-cause mortality, disenrollment from health plan, or end of study period (June 31, 2018). Consistent with the observational analog of the intention-to-treat approach, treatment changes after index date were disregarded. Crude occurrence of the main outcome of interest was summarized using cumulative incidences and incidence rates at 1 year.

To adjust for measured confounding at the time of COPD diagnosis, we developed a propensity score for antipsychotic drug use with prespecified covariates selected using subject matter knowledge.[21] We then fitted a Cox proportional hazards model conditional on the propensity score as a linear and quadratic term to estimate the effect of antipsychotic prescription compared to benzodiazepine use on the hazard of blood stream infections during follow-up. The 95% CIs were obtained via non-parametric bootstrapping with 2,000 samples. Finally, we assessed covariate balance and obtained adjusted survival curves using inverse probability weighting based on the propensity score.[22] Of note, bloodstream infections within the first week of antipsychotic or benzodiazepine use were not considered to avoid reverse causation.[23]

Sensitivity Analysis

Several sensitivity analyses were conducted to evaluate the robustness of our findings. First, we refitted our analysis including only the 4 most commonly prescribed antipsychotic drugs.[6] Second, we repeated the analyses

Figure 1. Flowchart of Study Patients



[a]Health care database of Hospital Italiano de Buenos Aires, index diagnosis of COPD captured from 2010 to 2015.
[b]Prevalent user defined as a patient with any antipsychotic or benzodiazepine use in the preceding 60 days of a COPD diagnosis.
[c]Six patients in the antipsychotic group and 1 patient in the benzodiazepine group are excluded from the analyses since they presented with the primary outcome within 7 days of therapy initiation.
Abbreviations: COPD = chronic obstructive pulmonary disease, ICS = inhaled corticosteroid, LABA = long-acting β-adrenergic agonist, LAMA = long-acting muscarinic antagonist.

in our cohort after exclusion of those concomitant users of both benzodiazepines and antipsychotics. Third, we performed our intention-to-treat analysis with a follow-up period of 30 days and with an extended follow-up period of 5 years. Fourth, we used the approach described by Fine and Gray[24] to model cause-specific hazards to explicitly handle competing risks by death. Fifth, we re-fitted our analysis comparing antipsychotics with high dopamine receptor (D_2) affinity to antipsychotics with a more sedative profile (eg, with additional affinities such as histaminergic or α receptors).[5] Sixth, we calculated the E-value for our main analysis to assess the degree of unmeasured confounding that would be needed to explain our main effect estimate.[25] Finally, we extracted the reason for the prescription of antipsychotics and benzodiazepine agents in the subset of our population in which the indication was readily available from clinical notes. We then included all indications in our propensity score model and recalculated our point estimates and 95% CIs.

We used STATA v.14.2 (2016; StataCorp LLC; College Station, Texas) for all analysis. All reported *P* values are 2-sided, and we used a threshold of .05 for statistical significance.

RESULTS

Overall, 2,514 adult patients were identified with a COPD diagnosis, of whom 930 met inclusion criteria and were included in the present report. The main reason for exclusion was absence of antipsychotic or benzodiazepine drug use (Figure 1). With exclusion of 7 individuals who presented with an event within 7 days of treatment initiation (6 receiving antipsychotics, 1 benzodiazepines), baseline clinical, demographic, and comorbidity information is presented in Table 1. Mean (SD) age was 75.0 (9.8) years, and 51.9% of patients were female. Of note, hypertension and tobacco use were the two most prevalent comorbidities, followed by depression, cardiac failure, and malignancy.

Several differences between groups at baseline were evident (judged by a standardized difference greater than 0.10), most notably in the case of age, cerebrovascular disease, dementia, and depression. Overall, antipsychotic users were older and had a higher prevalence of such comorbid conditions (Table 1). However, all standardized mean differences were below 10% after confounder adjustment (Supplementary Table 1).

Finally, mean (SD) time from COPD diagnosis to antipsychotic prescription was 3.2 (2.4) years and from

Table 1. Baseline Characteristics of Study Patients[a]

Baseline Characteristic	Entire Cohort (n = 923[b])	Antipsychotic Use (n = 366)	No Antipsychotic Use[c] (n = 557)	SMD[d]
Demographics				
Age, mean (SD), y	75.0 (9.8)	76.3 (9.6)	74.1 (9.9)	0.23
Female	479 (51.9)	182 (49.7)	297 (53.3)	0.07
Past hospital admissions, median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	0.08
Baseline comorbid disease				
Cerebrovascular disease	94 (10.2)	49 (13.4)	45 (8.1)	0.17
Anxiety disorder	89 (9.6)	33 (9.0)	56 (10.0)	0.04
Active malignancy	206 (22.3)	75 (20.5)	131 (23.5)	0.07
Diabetes mellitus	166 (18.0)	79 (21.6)	87 (15.6)	0.15
Dementia	72 (7.8)	50 (13.7)	22 (3.9)	0.35
Depression	313 (33.9)	154 (42.1)	159 (28.5)	0.29
Hypertension	710 (76.9)	283 (77.3)	427 (76.7)	0.02
Myocardial infarction	190 (20.6)	79 (21.6)	111 (19.9)	0.04
Heart failure	217 (23.5)	98 (26.8)	119 (21.4)	0.13
Chronic kidney disease	123 (13.3)	48 (13.1)	75 (13.5)	0.01
Past smoker	720 (78.0)	291 (79.5)	429 (77.0)	0.06
COPD treatment				
Long acting β-agonists	614 (66.5)	257 (70.2)	357 (64.1)	0.13
Long acting muscarinic antagonists	278 (30.1)	101 (27.6)	177 (31.8)	0.09
Inhaled corticosteroids	726 (78.7)	300 (82.0)	426 (76.5)	0.14
Defined daily doses[e]				
Low (≤ 0.25)	576 (62.4)	270 (73.8)	306 (55.5)	0.93
Medium (0.26–0.50)	143 (15.5)	43 (11.7)	100 (18.1)	0.12
Medium high (0.51–1.00)	113 (12.2)	34 (9.3)	79 (14.3)	0.18
High (> 1.00)	84 (9.1)	18 (4.9)	66 (12.0)	0.85

[a]Values are shown as n (%) unless otherwise noted.
[b]Six patients in the antipsychotic group and 1 patient in the benzodiazepine group were excluded from the analyses since they presented with the primary outcome within 7 days of therapy initiation.
[c]Reference group comprised benzodiazepine users.
[d]Absolute values of SMD (before confounder adjustment).
[e]One patient was without information on daily doses of antipsychotic drugs, and 6 patients were without information on daily doses of benzodiazepine drugs; 217 received quetiapine, 56 received olanzapine, 176 received risperidone, and 77 received haloperidol.
Abbreviations: COPD = chronic obstructive pulmonary disease, IQR = interquartile range, SMD = standardized mean difference.

Table 2. Participant Follow-Up Information

Variable	Antipsychotic Use (n = 366[a])	No Antipsychotic Use (n = 557[b])
Median follow-up, d	365	365
Bacteremia, cumulative incidence at 1 year, n (%)	22 (6.0)	13 (2.3)
Bacteremia, incidence rate per 10,000 person-days	1.93	0.69

[a]Six patients in the antipsychotic group and 1 patient in the benzodiazepine group were excluded from the analyses since they presented with the primary outcome within 7 days of therapy initiation.
[b]All patients included in the No Antipsychotic Use group were exposed to benzodiazepines (reference group, active control).

COPD diagnosis to benzodiazepine prescription was 1.06 (1.5) years. Second-generation agents were more frequently used than first-generation antipsychotics, and 33.1% of patients in the exposed group received prescription for 2 or more antipsychotics during follow-up. The most frequently used agents were quetiapine and risperidone, prescribed to 56.3% and 44.8% of antipsychotic drug users, respectively. Of note, 73.8% and 55.5% were exposed to low doses of antipsychotic and benzodiazepine agents, respectively (Table 1). The main reason for antipsychotic use was delirium (33.6%), followed by dementia-related agitation (17.0%) and depressive and anxiety disorders (14.3%; Supplementary Table 2).

Primary Analysis

A total of 35 bloodstream infections occurred during the first year of follow-up. Follow-up was complete for all patients in both study groups, and median follow-up was 365 days (Table 2). Incidence rates were 1.93 per 10.000 person-days in the antipsychotic and 0.69 per 10.000 person-days in the benzodiazepine group. Cumulative incidence at 1 year of follow-up was 6.0% and 2.3% in the antipsychotic and benzodiazepine groups, respectively (Table 2). The most frequent source of infection was pulmonary and urinary tract for gram-positive and gram-negative bacteria, respectively (Supplementary Table 3).

Finally, the use of antipsychotics was associated with a higher risk of bloodstream infections during the first year of follow-up. Specifically, the adjusted hazard of bloodstream infections for antipsychotic drug users was 2.41 (95% CI, 1.13 to 5.14) times the hazard for benzodiazepine users during the first year of follow-up from first prescription of the corresponding drug. Adjusted survival curves are presented in Figure 2. The bacteremia-free survival was 97.4% (95% CI, 96.4 to 98.5) and 94.2% (95% CI, 91.5 to 96.9) for the benzodiazepine and antipsychotic groups, respectively.

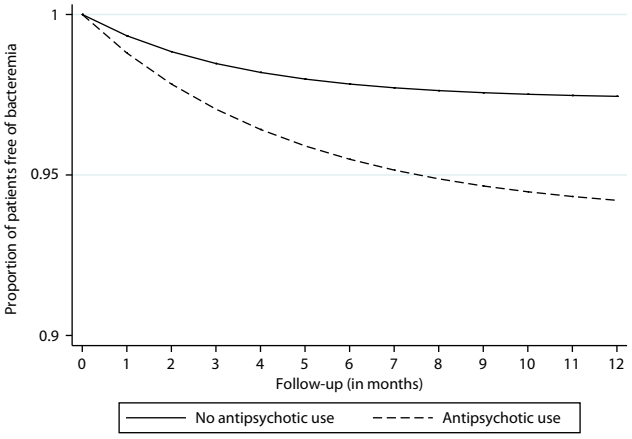
Sensitivity Analyses

Our results were robust to multiple sensitivity analyses (Supplementary Table 4). Specifically, similar results were

yielded by our analysis considering the competing risk of death. The cause-specific hazard ratio (HR) of bloodstream infections during the first year of follow-up was 2.31 (95% CI, 1.11 to 4.80) when comparing incident antipsychotic to incident benzodiazepine users.

The use of agents with a higher affinity for the D_2 dopaminergic receptor (ie, haloperidol and risperidone) was associated with a higher risk of bloodstream infections during the first year of follow-up when compared to use of sedative antipsychotic agents with lower D_2 affinity, such as olanzapine and quetiapine (HR = 5.20; 95% CI, 1.53 to 17.67). Furthermore, similar estimates were evident when changing the follow-up timeframe, when fitting a marginal structural model, and when adjusting for the specific recorded reason for prescription of either antipsychotics or benzodiazepines (Supplementary Table 4). Finally, the E-value for our main effect point estimate was 3.02, while the E-value for the lower bound of the corresponding confidence interval was 1.51).

Figure 2. Adjusted Survival Curves[a]



[a]Inverse probability weighting of a pooled logistic regression to approximate a Cox proportional hazards model.

DISCUSSION

Our study offers preliminary evidence that antipsychotic agents are associated with incident bloodstream infections in adult patients with COPD during the first year of follow-up. Moreover, this association appears to be stronger in agents with a higher dopamine receptor affinity, such as risperidone or haloperidol. To our knowledge, this study is the first to report the association between antipsychotic drug exposure and the risk of bloodstream infections.

There is mounting evidence—derived mainly from studies in patients with schizophrenia and in vitro models—suggesting that antipsychotic drugs may modify the immunologic response by a variety of mechanisms, including changes in macrophage activation and decreased levels of proinflammatory cytokines.[26] This modulation of immunologic response may be specially relevant with haloperidol or risperidone treatment.[27] Moreover, the inhibition of tumor necrosis factor–alpha (TNF-α) production, natural killer cell activity, and antibody-dependent cell-mediated cytotoxicity in a dose-dependent manner has been described with sedative agents such as chlorpromazine.[28] Drug-induced obesity and insulin resistance have also been proposed as mediators of immunomodulation, since lower serum levels of proinflammatory cytokines have been linked to these conditions, though a direct effect on the reduction of proinflammatory cytokines levels with olanzapine and aripiprazole has also been described.[29] Our findings are consistent with these previous reports and add relevant information on the risk of clinically meaningful outcomes for adult patients who start a new antipsychotic agent. However, since our study was conducted under real-world conditions and measurement of cytokine levels is not part of routine follow-up studies in our institution, we could not include this parameter as part of our analysis. Thus, future studies accounting for changes in the peripheral levels of cytokines and the occurrence of bloodstream infections remain warranted. In this regard, the choice of patients with COPD likely enhanced the observed deleterious effect of antipsychotics, since these patients remain at higher risk of lower respiratory tract and invasive infections by mechanisms related to the underlying pulmonary disease, systemic compromise, and corticosteroid therapy.[30]

Moreover, our analysis suggests that a higher risk of bloodstream infections with those antipsychotics with a higher D_2 dopamine receptor affinity such as haloperidol and risperidone may shed light on the underpinnings of the estimated effect (ie, a direct dopaminergic effect on cytokine levels rather than a secondary effect mediated by drug-induced obesity or insulin resistance). If confirmed by future studies, this proposed mechanism not only would point toward a potential pathway including dopaminergic changes as a likely mechanism but also may affect the individual prescription patterns of those patients who are considered for antipsychotic therapy but present high risk of invasive infections based on their overall burden of comorbid disease. Nevertheless, the overall low proportion of new users of clozapine—that is, a drug with mounting evidence of increased risk for several infections[9,31–33]—in our study population must be considered when analyzing our findings. Additional studies specifically evaluating the effect of clozapine use on the risk of bloodstream infections are needed to further confirm our findings and evaluate potentially different effects of specific antipsychotics.

Several limitations must be considered when evaluating our findings. First, owing to the observational nature of our data, both residual and unmeasured confounding may at least partially explain our effect estimates. However, we captured extensive baseline information on potential known confounders and factors potentially associated with bloodstream infections (ie, sex, malignancy, tobacco use, chronic renal failure, though with the exception of severity of COPD disease) considered a priori. In addition, we developed an active control and new user design as a strategy to further decrease the likelihood of

baseline confounding by indication by both measured and unmeasured covariates.[34,35] Furthermore, our E-value suggests moderate robustness to unmeasured confounding, and our findings were consistent across a wide spectrum of sensitivity analyses. Second, we measured only baseline comorbidities and covariates and thus could not assess for time-varying confounding. Nevertheless, we limited our main analysis to the estimation of the intention-to-treat effect and a relatively short 1-year follow-up period, likely rendering our main analysis an unbiased estimate of the effect of prescription patterns at baseline. Third, we could not precisely define the duration and adherence to treatment for each patient and the time interval between the last dose of antipsychotics and onset of bacteremia, given the administrative nature of our database. However, as measures to mitigate these limitations, we defined an extensive time period free of antipsychotic and benzodiazepine prescription prior to the diagnosis of COPD to identify new users and also restricted the considered follow-up period in our main and sensitivity analyses (at 30 days and 5 years of follow-up). These actions were taken to evaluate potential misclassification of patients as exposed to antipsychotics or benzodiazepine drugs during long-term follow-up, yielding similar findings across the different analyses. It is worth noting that assuming that antipsychotic drugs do increase the risk of bloodstream infections, misclassification of patients as antipsychotic drug users would likely bias our results toward the null, thus increasing the confidence in our effect estimates. Fourth, immunomodulatory effects of antipsychotic drugs have been described in populations in which higher therapeutic doses are achieved than the ones observed in our study (ie, in patients with severe mental illness). Nonetheless, if the effect appears evident among patients with low-level exposure, the impact of these drugs on the immune system may be greater than described in this article. Fifth, given the known association of antipsychotics with all-cause mortality, the competing risk of death and consequent selection bias should be acknowledged. However, our sensitivity analysis estimating the cause-specific hazard ratio yielded very similar causal effect estimates. Finally, our choice of adult patients with COPD may render our findings not generalizable to other populations with varying risk of severe infections at baseline and potentially different distribution of effect modifiers.

Conversely, several strengths of the present study are worth highlighting. To our knowledge, this study is the first to evaluate and report the increased risk of bloodstream infections following the use of antipsychotic agents. Furthermore, it also extends the previously available knowledge of excess of risk of infections with antipsychotic drugs to a population different from that of patients with schizophrenia or dementia. Finally, we developed several strategies to tackle limitations inherently related to cohort studies. First, since any comparison between initiators and non-initiators of a drug using observational data is challenging, not only due to confounding by indication, but also because factors such as health-seeking behaviors, accuracy in the measurement of covariates, and access to health are expected to differ between groups, we decided to use an active control (such as benzodiazepines) to account for these variables.[33] Second, we used propensity score estimation and inverse probability weighting to account for a broad range of confounders. Finally, we performed multiple sensitivity analysis with consistent results.

In conclusion, our study offers preliminary data suggesting that the use of antipsychotic agents may increase the risk of bloodstream infections in adult patients with COPD. This risk may be higher with the use of agents with a more potent dopaminergic antagonism. Our results suggest a potential immunomodulatory effect of antipsychotic agents. Further studies are warranted to confirm our findings and to explore the underlying mechanisms and the effect in distinct populations and settings. In particular, it would be of interest to evaluate this effect in patients with a primary psychotic disorder and incorporate a wider range of antipsychotic agents (eg, clozapine).

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Supplementary material: Available at PSYCHIATRIST.COM.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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Supplementary Material

Article Title: Antipsychotic Use and Bloodstream Infections Among Adult Patients With Chronic Obstructive Pulmonary Disease: A Cohort Study

Author(s): Augusto Ferraris, MD; Belén Blasco, MD; Nicolás Tentoni, MD; Facundo Del Olmo, MD; Tomás Barrera, MD; Federico Angriman, MD, MPH; and Alejandro G. Szmulewicz MD, MPH

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Antipsychotic Use and Bloodstream Infections among Adult Patients with Chronic Obstructive Pulmonary Disease: A Cohort Study

Supplementary Table 1. Standardized differences of main characteristics after inverse probability weighting

Baseline characteristic	SMD[a]
Age, years	0.005
Past hospital admissions	0.006
Cerebrovascular disease	0.008
Active malignancy	0.001
Diabetes mellitus	0.002
Dementia	0.006
Myocardial infarction	0.001
Inhaled corticosteroids	0.001

a. Absolute values. SMD: Standardized mean differences between patients who were prescribed antipsychotics or benzodiazepines

Supplementary Table 2. Indications for new antipsychotic and benzodiazepine drugs users.

Indications for antipsychotic or benzodiazepine drugs, no. (%)[a]	Entire cohort (n=923)	Antipsychotic use (n=366)	No antipsychotic use[b] (n=557)
Delirium - continued treatment after hospital discharge	158 (17.1)	123 (33.6)	35 (6.3)
Dementia related psychosis or agitation	77 (8.3)	62 (17.0)	15 (2.7)
Depressive and anxiety disorders	259 (28.1)	52 (14.3)	207 (37.2)
Sleep-wake disorders	182 (19.7)	38 (10.4)	144 (25.9)

a. Indications for prescription were identified by review of electronic medical charts when available. Indications for antipsychotic or benzodiazepine drugs were not exclusive (patients could present multiple indications for the same drug at the time of prescription).
b. Reference group comprised by benzodiazepine users.

Supplementary Table 3. Description of blood stream infections at one year of follow up

Source of infection	Gram negative bacteremia (n=25)	Gram positive bacteremia (n=10)
Urinary tract infection	11	1
Lower respiratory tract infection	5	5
Intra-abdominal sepsis	4	1
Bacteremia with unclear source	3	1
Other source (bone, central nervous system)	2	2

Supplementary Table 4. Summary of sensitivity analysis

	Hazard ratio (95% CI)
Restricted to highly used antipsychotics (i.e., haloperidol, quetiapine, olanzapine, risperidone)[a]	2.42 (1.10 - 5.33)
Excluding users of both benzodiazepine and antipsychotics during follow-up[a]	1.72 (0.66 - 4.48)
Follow-up up to 5 years[a]	1.65 (0.99 - 2.75)
Follow-up up to 30 days[a]	1.86 (0.60 - 5.75)
Fine & Gray sub-distribution hazard model[b]	2.31 (1.11 - 4.80)
Marginal structural Cox proportional model[c]	2.30 (1.12 - 4.74)
Comparing pure D2 antagonists to sedative antipsychotics[a,d]	5.20 (1.53 - 17.67)
Including the indication for antipsychotic or benzodiazepine drugs[a,e]	1.41 (0.56 - 3.63)

a. Cox proportional hazards model conditional on the propensity score, b. Sub-distribution hazard ratio to account for the competing risk of death
c. Inverse probability of treatment weighting using stabilized weights.
d. Pure D2 antagonists: risperidone and haloperidol. Sedative antipsychotics: mostly quetiapine and olanzapine based on local practice.
e. Indications for prescription were identified by review of electronic medical charts when available.
Abbreviations: CI: confidence interval