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ORIGINAL RESEARCH

Breath and Bottle: Evaluating Pharmacotherapy for Alcohol Use Disorder on COPD Exacerbation Outcomes

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Background: The role of pharmacotherapy for alcohol use disorder (AUD) in mitigating COPD exacerbations remains under-explored. This study aims to evaluate the impact of AUD pharmacotherapy on COPD-related clinical outcomes.

Methods: A retrospective cohort study was conducted on 635 COPD patients with comorbid AUD. Patients were categorized into two groups based on whether they received medication for AUD (MAUD group) or not (no-MAUD group). Data on demographics, COPD severity, exacerbation rates, and AUD treatment were extracted from electronic medical records.

Results: Individuals in the MAUD group (n=229) exhibited a substantially reduced frequency of COPD exacerbations when compared to those in the non-MAUD group (n=406), with a significant difference observed (P<0.001). Additionally, the MAUD group experienced a longer duration before the first exacerbation event (P<0.001).

Conclusion: Pharmacotherapy for AUD appears to have a protective effect against the occurrence of COPD exacerbations and improved clinical outcomes in patients with comorbid AUD. These findings suggest that AUD treatment should be considered as part of a comprehensive management strategy for COPD patients with AUD.

Keywords: alcohol use disorder, chronic obstructive pulmonary disease, exacerbation, addiction treatment

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic respiratory disease, affecting 213.4 million individuals worldwide, with China alone reporting a prevalence of 8.6% in adults.[1] Environmental exposures and comorbid conditions, have been implicated in the pathogenesis of COPD exacerbations.[2,3] Alcohol consumption are strongly associated with an elevated risk of adverse clinical outcomes, particularly in patients requiring hospitalization or emergency interventions. Alcohol use disorder (AUD) is characterized by persistent patterns of excessive alcohol consumption despite adverse health or social consequences, leading to impaired control over intake and heightened vulnerability to comorbid conditions such as COPD.[4] In subpopulations of COPD patients with comorbid AUD, the risk of hospital readmission is significantly heightened, with a 1-year post-discharge mortality rate of 22%.[5]

As with other alcohol-related health conditions, complete abstinence from alcohol remains the cornerstone of optimal management, though achieving this goal is often challenging.[6] In contrast, Pharmacotherapeutic interventions for alcohol dependence, however, have demonstrated efficacy in achieving and sustaining abstinence among patients with AUD.[7] Addiction treatment modalities also play a critical role in mitigating the progression of AUD-related comorbidities.[8] Nevertheless, the potential role of AUD pharmacotherapy in preventing COPD exacerbations remains poorly understood.

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Given the potential benefits of addiction pharmacotherapy for COPD patients with co-existing AUD, this study aims to evaluate differences in COPD-related clinical manifestations (eg, lung function, time to first exacerbation, and hospitalization rates) between COPD patients with co-existing AUD who receive addiction treatment and those who do not. The study was designed to explore whether AUD medication could effectively slow COPD progression, reduce the risk of exacerbation, and improve patients' quality of life. Through this study, we hope to provide more concrete basis for clinical treatment and how to comprehensively consider addiction treatment to optimize the management of COPD.

Methods

Data Sources

This retrospective cohort study included patients admitted to the psychiatry, health checkup, emergency, and internal medicine departments of The Affiliated Encephalopathy Hospital of Zhengzhou University from January 1, 2015, to December 1, 2024. The study included individuals diagnosed with COPD who exhibited high-risk alcohol consumption. Data were extracted retrospectively from the hospital's electronic medical records system. Data collected included patient demographic characteristics, clinical diagnosis of COPD, records of acute exacerbations and length of hospital stay, spirometry data, severity and scores of COPD-related symptoms and dyspnea, activities of daily living, exercise tolerance, and AUD questionnaire results. The study employed an opt-out methodology for patient enrollment, in accordance with institutional ethical guidelines. This study complied with the Declaration of Helsinki and was approved by the Affiliated Encephalopathy Hospital of Zhengzhou University Research Ethics Committee (Approval No. 2024–001-01). Patient data confidentiality was strictly maintained, with anonymized records used for analysis. The Institutional Review Board granted a waiver for informed consent, considering the retrospective nature of our study.

Patients were included if they had: (1) Patients were included if they met the following criteria: (1) high-risk drinking, defined as an Alcohol Use Disorder Identification Test (AUDIT-C) score of >8, and (2) a diagnosis of AUD among incident COPD patients.[9] Patients were excluded for the following reasons: (1) death or no follow-up within one year of COPD diagnosis, (2) use of AUD medications in the year prior to COPD diagnosis, and (3) age under 18 years or over 90 years at the time of COPD diagnosis. (4) patients suffering from bronchial asthma, bronchiectasis, cystic fibrosis, or cancer.[10] (5) during the study period or reversal of COPD diagnosis within 3 months.[11] Patients meeting the criteria were categorized into two groups based on whether they received medication for alcohol use disorder (MAUD): (1) the MAUD group and (2) the no-MAUD group.

Exposure

Patients who received medication for AUD disulfiram, acamprosate, naltrexone, gabapentin, topiramate, varenicline or baclofen for at least 7 days within 30 days of the diagnosis of COPD were considered to be in the exposed group (MAUD group).[12]

Covariates

Clinically important confounders were selected, including age (>70 years), body mass index (<18.5, >25 kg/m^2), history of previous hospital admission for COPD, exercise tolerance and dyspnea, mental status on admission, History of using nicotine as well as other nonalcoholic substances, and receipt of non-pharmacological psychotherapy.[13]

Outcomes

The primary end point was the time to the first COPD acute exacerbation. Acute exacerbations of COPD were categorized as either moderate or severe. Specifically, according to the Rome proposal's standardized thresholds, exacerbations were classified as moderate if they required treatment with short-acting bronchodilators in combination with antibiotics and/or oral corticosteroids. In contrast, exacerbations were deemed severe if they necessitated a visit to the emergency department or hospitalization due to a significant worsening of the patient's condition.[14] If more than 2 acute exacerbations of any severity were identified within 14 days, the events were counted as the same event, and the

date of the acute exacerbation was recorded as the date of the first acute exacerbation. Secondary end points included the annual rate of moderate to severe exacerbations, lung function, length of hospital stay, quality-of-life scores, and survival.

Statistical Analysis

For continuous variables, comparisons between the two groups were conducted using either the independent samples *t*-test (for normally distributed data) or the Mann–Whitney *U*-test (for non-normally distributed data). Categorical variables were assessed using the Chi-square test or Fisher's exact test, as appropriate. Kaplan-Meier curves were utilized to depict time-to-event data, with differences analyzed using the Log rank test. Cox proportional hazards regression was employed to estimate hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for the time to first exacerbation between the two groups. A *P*-value threshold of <0.05 was set to determine statistical significance. All statistical analyses were performed using SAS® version 9.4. The proportional hazards assumption was evaluated using Schoenfeld residuals to ensure no time-dependent covariate effects. The multicollinearity among covariates was assessed by calculating variance inflation factors. The model fit was examined via the Akaike Information Criterion and log-likelihood ratio tests to compare nested models.

To address potential confounding, propensity scores were calculated. These scores represented the probability of a patient being prescribed a specific medication for AUD, estimated using a logistic regression model that adjusted for known confounders. The propensity scores were derived using baseline covariates through multivariable logistic regression analysis.

Results

Patient Characteristics

Following application of the selection criteria (Figure 1), 635 patients (7.1%) from a total of 8,939 COPD patients were included in the final analysis cohort. The patients were mainly male (n=569, 89.6%), with a mean age of 57.4 years. Of these, 229 patients had received at least 7 days of AUD treatment following their COPD diagnosis. 13.1% patients received treatment for > 3 months. The duration of AUD treatment was <3 months 199 cases (86.9%). The average age of MAUD group was 58.1 years, of which 89.1% (n = 204) were 50–70 years old. The mean age of patients in the no-MAUD group was 57.0 years, with 87.5% (n = 355) of patients aged between 50 and 70 years. (Table 1). Among patients treated with AUD, 105 (45.9%) used disulfiram, 77 (33.6%) were exposed to naltrexone, 16 (7.0%) received acamprosate, and 31 had used more than two drugs. During follow-up, cessation events included death (5 patients, 0.8%), loss to follow-up (defined as no medical contact for >12 months; 23 patients, 3.6%), and administrative censoring at the study cutoff date (December 1, 2024). All events were right-censored in survival analyses to avoid bias in estimating time-to-first exacerbation.

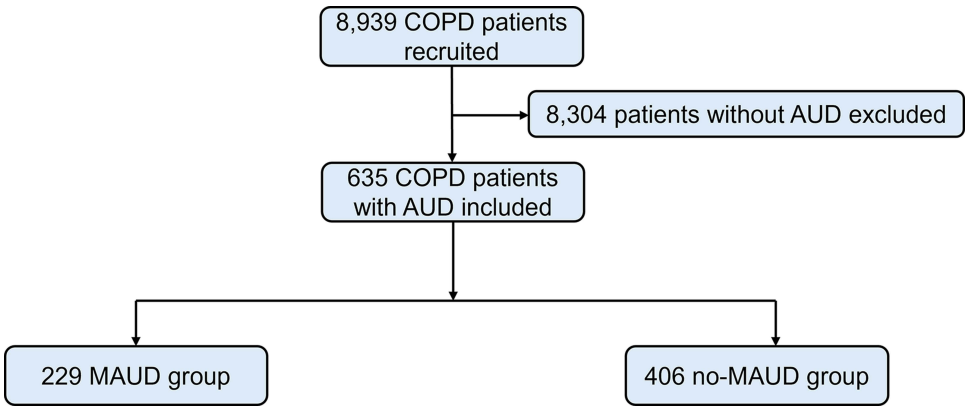

Figure 1 Flowchart of patient selection.

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Table 1 Characteristics of Subjects Presenting to the COPD Patients with AUD

Characteristic	No. (%)			*P* value
	All Patients	Medical Addiction Therapy		
		MAUD Group	No-MAUD Group	
No.	635 (100)	229 (36.1)	406 (63.9)	NA
Age, mean (SD)	57.4 (13.5)	58.1 (15.3)	57.0 (13.7)	0.37
Sex				
Female	66 (10.4)	18 (7.9)	48 (11.8)	0.11
Male	569 (89.6)	211 (92.1)	358 (88.2)	0.31
BMI, mean (SD)	27.8 (5.4)	28.1 (6.2)	27.6 (7.5)	0.36
Receipt of psychotherapy	250 (39.4)	175 (76.4)	75 (18.5)	<0.001
Smoking	203 (31.9)	68 (29.7)	135 (33.3)	0.35
Hospitalization within 90 days	459 (72.3)	168 (73.4)	291 (71.7)	0.64
Independent of daily living	15 (2.3)	2 (0.8)	13 (3.2)	0.06

Abbreviations: SD, standard deviation. BMI, body mass index. NA, not applicable. MAUD, medication for alcohol use disorder.

Factors Associated with Receipt of MAUD

In the multivariate regression model, the confounders most closely associated with the use of AUD medications included age, sex, body mass index (BMI), smoking status, activities of daily living, history of pulmonary function testing, history of hospitalization, mental status, use of psychotropic medications, and comorbidities. To ensure optimal matching between the two groups, we initially computed propensity scores using a probit regression model based on the covariates outlined earlier. Subsequently, we assessed the balance of observed covariates through a love plot, utilizing the standardized mean difference (SMD) as a metric. A threshold of $|SMD| < 0.1$ was adopted to indicate satisfactory balance (Figure 2). The covariates included in the propensity score model were selected based on their established clinical relevance to both AUD management and COPD outcomes. Adjusting for these factors allows for a more robust estimation of the specific effect of AUD pharmacotherapy on COPD exacerbations, independent of these important clinical characteristics.

Incidence of Acute Exacerbations of COPD After Medical Addiction Therapy

We present the condition of COPD exacerbations in the MAUD and no-MAUD groups (Table 2). A total of 173 patients had an exacerbation of COPD. There were 42 patients in the MAUD group, 12 of whom had severe exacerbations. In the no-MAUD group, 126 patients had exacerbations, and a higher proportion had severe exacerbations (P=0.03), with 41 having to be hospitalized. The annual rate of acute exacerbation (number of episodes/patient/year) in MAUD group was significantly lower than that in no-MAUD group. The difference between MAUD group and no-MAUD group in the occurrence of COPD exacerbation was 12.7% (P<0.001). The unadjusted odds ratio (OR) for the MAUD group compared with the no-MAUD group was 0.49 (95% CI: 0.41–0.57). And after weighting propensity scores, we found that adjusted OR was 0.43 (95% CI: 0.38–0.55). Regarding respiratory support, COPD patients who did not undergo AUD treatment were more frequently documented with respiratory failure and had a higher likelihood of requiring mechanical ventilation upon arrival (P<0.001). In contrast, COPD patients receiving medical treatment for AUD exhibited higher partial pressures of oxygen (P<0.001) and lower partial pressures of arterial carbon dioxide (P<0.001).

In a multivariate analysis, we found that any medical treatment for AUD was associated with reduced odds of COPD exacerbations (Table 3). And receiving naltrexone (OR= 0.41), disulfiram (OR=0.37), or acamprosate (OR=0.55) was independently associated with decreased odds of COPD exacerbations.

Association Between AUD Medications and Time to First Exacerbation

The time interval from 30 days post-diagnosis to the first COPD exacerbation was assessed among patients with AUD. After adjusting for follow-up duration using Cox proportional hazards regression, the time to first exacerbation was found

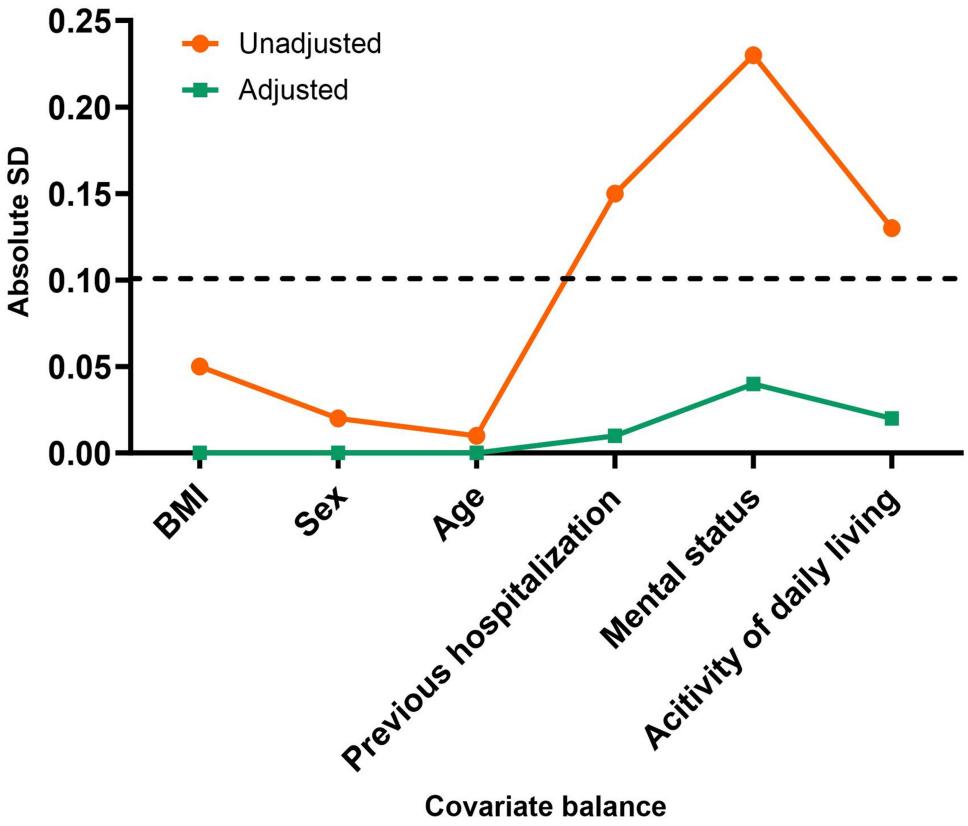

Figure 2 Clinical relevance of covariate balance after matching. Standardized mean differences (SMD) demonstrate successful balancing of key clinical factors between MAUD and non-MAUD groups after propensity scoring (all |SMD| <0.1).

to be significantly longer in the MAUD group compared to patients who did not receive addiction treatment (P<0.001). The median time to the first exacerbation was 38.5 months in the MAUD group and 26.9 months in the no-MAUD group (unadjusted hazard ratio (HR) 0.78, adjusted HR 0.72, Table 4). In the moderate and severe exacerbation subgroups, the

Table 2 Outcomes of COPD Patients with Co-Existing AUD in Two Groups

	No. (%)			P value
	All Patients (n=635)	MAUD Group (n=229)	No-MAUD Group (n=406)	
Moderate exacerbation	115	30	85	0.014
Severe exacerbation	58	12	41	0.033
Hospitalization duration (days)	7.5	6.5	8.0	<0.001
Maximal oxygen requirement (L/min)	4.2 (2.5)	4.5 (1.3)	4.1 (2.9)	0.017
pO_2 (mmHg)	72.9 (7.4)	78.2 (9.2)	69.9 (14.1)	<0.001
pCO_2 (mmHg)	35.7 (3.2)	32.4 (4.6)	37.5 (4.5)	<0.001
Died (in total)	5	1	4	0.45

Abbreviations: pO_2, partial pressure of oxygen, pCO_2, partial pressure of arterial carbon dioxide.

Table 3 Odds Ratios for the COPD Exacerbations After Addiction Treatment

Addiction Treatment	Odds Ratio (95% CI)	*P* value
Any pharmacotherapy	0.43 (0.32–0.56)	<0.001
Disulfiram	0.37 (0.31–0.47)	0.04
Naltrexone	0.41 (0.36–0.76)	0.01
Acamprosate	0.55 (0.39–0.88)	0.03

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Table 4 Hazard Ratios for COPD Exacerbations

	Hazard Ratio (95% CI)	
	Unadjusted	**Adjusted**
Moderate	0.75 (0.67, 0.84)	0.76 (0.63, 0.78)
Severe	0.81 (0.65, 0.89)	0.80 (0.70, 0.91)
Total	0.78 (0.69, 0.86)	0.72 (0.66, 0.82)

time to the first exacerbation was longer in the MAUD group than in the no-MAUD group, similar to the results overall. The adjusted HR was consistent with the unadjusted HR. The proportional hazards assumption was assessed via Schoenfeld residuals (P=0.15). No significant time-dependent effects were detected, confirming the robustness of the Cox model.

Discussion

This retrospective study sought to evaluate the association between AUD pharmacotherapy and the risk of future COPD exacerbations. Our findings indicate a significantly reduced annualized exacerbation rate among COPD patients with comorbid AUD who received addiction pharmacotherapy. In patients with COPD, excessive alcohol consumption may exacerbate the clinical manifestations of the disease. Alcohol not only directly damage the lung immune system and aggravate respiratory tract inflammation, but also aggravate COPD symptoms by affecting patients' smoking behavior, medication compliance and disease management.[15] However, previous randomized controlled trials for COPD excluded patients with AUD, little is known about the role of AUD pharmacotherapy in the prevention of exacerbations in COPD patients. Our study adds to this gap in the therapeutic field. In this cohort study, patients treated with disulfiram had the lowest rates of COPD exacerbations during follow-up. In addition to its effect on reducing alcohol intake, disulfiram also has anti-anxiety effects.[16] Given the underuse of addiction treatment in COPD patients, we believe that the results of this study highlight the importance of addiction treatment in COPD patients with AUD.

The underlying biological mechanism for the protective effect of MAUD on COPD exacerbations observed in this study may be related to the blocking of multiple harmful effects of alcohol on the respiratory system. The detrimental effects of alcohol on COPD progression are mediated through multiple interconnected biological pathways. Chronic alcohol consumption impairs alveolar macrophage function. This immune dysfunction increases susceptibility to respiratory infections.[17] This immune suppression is further exacerbated by alcohol-induced depletion of glutathione, leading to elevated reactive oxygen species levels that damage airway epithelium and amplify neutrophilic inflammation.[18] A critical synergy exists between alcohol and smoking, while combined exposure upregulates matrix metalloproteinases, accelerating emphysematous alveolar destruction.[19] Additionally, alcohol also interferes with COPD therapies, pharmacokinetic interactions may occur, as alcohol competes with CYP450-mediated drug metabolism, altering the clearance of theophylline.[20]

The high recurrence rate of AUD necessitates long-term medical intervention.[21] In this study, the group of patients with COPD and AUD was likely to be in a highly frail state.[22] AUD not only directly aggravate the physiological burden of COPD, but also its accompanying mental health problems and social dysfunction, further damage the patient's self-management ability and treatment compliance. Frailty may be an important reason for its high readmission rate and poor prognosis. In addressing the healthcare needs of patients with both obstructive lung disease and AUD, AUD treatment emerges as a promising strategy to enhance healthcare utilization efficiency within this vulnerable patient population.[23] Therefore, AUD pharmacotherapy has the importance of synergistically addressing physical and psychosocial factors of frailty.

Our study provides evidence that treatment of addictive drugs can improve the prognosis of patients with COPD and is expected to save the health care system the cost of treating related comorbidities. Compared with resource-intensive cognitive behavioral interventions for AUD and associated comorbidities, pharmacological interventions can be used as

a treatment that can be easily implemented and expanded.[24] This is particularly important given the shortage of available resources for mental health and addiction intervention treatment.[25] Our research will be instrumental in refining clinical guidelines and optimizing therapeutic interventions for this complex patient population.

However, the current literature presents limitations in detailing the prevalence of acute COPD exacerbations among these patients. The criteria for diagnosing acute exacerbations are often inconsistently applied, leading to ambiguity in the reported incidence rates. This gap underscores the necessity for future prospective studies to elucidate the specific subgroups of patients who stand to gain the most from combined treatment strategies.

Our observational study has some limitations. First, the retrospective study cohorts were underrepresented. Although we accounted for a variety of confounding factors in the multivariate analyses, there were geographic limitations, and the participants may not be representative of the general population. Longitudinal evaluation is essential to determine the protective effect of AUD pharmacotherapy on lung function.[26] Longitudinal data need to be collected frequently over a considerable period of time, but it is difficult to reduce the risk of recall bias in this study. Second, our primary objective was to concentrate on the highest-risk cohorts that could potentially benefit from addiction treatment. The cases we analyzed were primarily characterized by moderate-to-severe AUD. Mild AUD cases might not have been fully identified or documented due to several factors. These factors include patients underreporting their alcohol consumption, apprehensions about the stigma associated with accurate alcohol reporting, and obstacles in systematically recording cases. Third, the impact of AUD on access to care, treatment availability, and treatment adherence is a notable limitation. This limitation may introduce statistical noise and bias into the analysis.

Conclusion

This study provides evidence of an association between AUD pharmacotherapy and a reduced incidence of COPD exacerbations. This study suggests that in the absence of contraindications to addiction treatment, clinicians may consider the use of addiction treatment for AUD as a means of preventing COPD exacerbations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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