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Six-Month Outcomes for Collaborative Care Management of Depression Among Smoking and Nonsmoking Patients

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Abstract

Background: Collaborative care management (CCM) is an evidence-based model that contributes to better outcomes for depression treatment in the primary care setting. Tobacco use increases overall economic costs, morbidity, and mortality and has been shown to impact behavioral health outcomes. Our study aims to observe clinical outcomes for depression treatment for patients with comorbid tobacco use and depression within the CCM model.

Methods: A retrospective chart review study of 2826 adult patients with depression enrolled in CCM was performed to determine the association between regular tobacco use and depression outcomes. Baseline intake data consisting of clinical and demographic variables along with 6-month follow-up of Patient Health Questionnaire-9 (PHQ-9) scores for smokers (n = 727, 25.7%) and nonsmokers (n = 2099, 74.3%) were obtained. Depression remission was defined as a PHQ-9 score <5 and persistent depressive symptoms (PDS) as a PHQ-9 score $\geq$10 at 6 months.

Results: Using an intention-to-treat analysis, the multivariate modeling demonstrated that smokers, at 6 months, had an increased adjusted odds ratio (AOR) for PDS: 1.624 (95% CI: 1.353-1.949). Furthermore, smokers had a lower AOR of depression remission: 0.603 (95% CI: 0.492-0.739). Patient adherence to treatment was also lower in smokers with an AOR of 0.666 (95% CI: 0.553-0.802).

Conclusions: Smokers enrolled in CCM were associated with reduced treatment adherence and worse outcomes for depression treatment at 6 months compared to nonsmokers, even when baseline clinical and demographic variables were controlled. Thus, new tailored practices may be warranted within the CCM model to treat comorbid depression and tobacco use disorders.

Keywords
primary care, addiction, depression, smoking, collaborative care management

Introduction

Depressive disorders account for the highest proportion of disability-adjusted life years out of all measured mental, neurological, and substance use disorders that account for years lost due to disability[1]; it is also the second leading cause of disability worldwide in 2010.[2] Depressive disorders commonly include major depressive disorder (MDD), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, and substance/medication-induced depressive disorder, among other presentations.[3] Depressive disorders are associated with a higher risk of smoking.[4] Smoking tobacco products is associated with an increased risk of chronic disease (eg, malignant neoplasms, cardiovascular diseases, and respiratory diseases), morbidity, and mortality[5] and is identified to be the leading cause of preventable deaths across the world.[4] While smoking

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among adults living in the United States has decreased from 42% to 15.1% over the past 50 years,[5,6] there continues to be a significant disparity in prevalence of smoking between individuals with and without serious mental illness; 53% of patients with a reported mental health disorder smoke tobacco products regularly.[7,8] A US population-based study suggested that individuals with mental illness are approximately twice as likely to smoke compared to individuals without mental illness.[9] Moreover, epidemiological studies found regular use smoking rates to be as high as 43% for those with MDD,[10] providing clear evidence that a higher proportion of patients with depressive disorders smoke (43%) compared to the general population in the United States (15.1%).

Strong correlations between comorbid depressive disorders and tobacco use disorder have been well documented in epidemiological studies,[11-20] but it remains debated as to the exact relationship between the 2 disorders. Either tobacco use disorder or depressive disorders are caused by common genetic and environmental risk factors, or they share a cause and effect relationship, where one condition precipitates the other. Studies have suggested that smoking and depressive disorders are correlated due to common environmental and genetic risk factors;[14,18,21-25] others have argued that tobacco use may arise as a result of self-medication of depressive symptoms[12,13,26] or that chronic use of tobacco products may have causal effect on the development of depressive symptoms.[14-16,27,28] Patients with depressive disorders are at increased odds for smoking and experience increased difficulties with smoking cessation, suggesting that preexisting depressive disorders can be associated with chronic nicotine dependence.[29,30] However, the opposite pathway is complicated by large Mendelian randomization studies which examine causal pathways between genetic markers for nicotine dependence and depressive disorders; these do not implicate smoking as a causal mechanism for developing first-time depressive episodes.[29,31-33] Abstinence from tobacco products without nicotine supplementation can also cause nicotine withdrawal syndrome, which can present with symptoms of a substance-induced depressive disorder, among other cognitive and emotional alterations.[34]

Treatment for depressive disorders in the United States has largely shifted from the psychiatrist's office to the primary care setting.[35] Primary care providers in the United States saw more patients with mental health-care needs and prescribed more of the total antidepressants used in 2006 to 2007 (62%) than psychiatrists (21%).[36] There has also been a history of failing to coordinate primary health care with advanced mental health care. In 1 US study, less than 50% of patients referred from primary care scheduled an appointment with a mental health specialist and less than 50% of scheduled appointments were actually attended.[37] Given the history of disconnect between primary care and specialized mental health care, many health systems have adopted integrated behavioral health models in the primary care setting.

In primary care settings, the provision of collaborative care management (CCM) has increased; CCM is an integrated behavioral health model which involves integrated care for depressed patients provided by a specially trained care manager, with cases overseen by psychiatry.[38-40] Collaborative care management relies on integrated care managers who establish care with the patient in the primary care office. Compared to usual care (UC), studies have found that CCM models have decreased the likelihood of remission of clinically significant depressive disorders, decreased the likelihood of having persistent depressive symptoms (PDS), and increased the likelihood of achieving improved workplace outcomes.[41-45] Multiple analyses suggested that responses to CCM occur as early as 6 to 12 weeks.[46,47] Moreover, patients with depressive disorders enrolled in CCM have been shown to have a 2.5 times higher likelihood of remission after 6 months of care than patients with depressive disorders treated in UC models, with a more rapid response rate to treatment over time.[48]

Numerous studies have identified smoking[49] and depressive disorders[50-52] as independent risk factors for patient nonadherence to medical treatment plans. It remains unclear whether smoking complicates the therapeutic picture and decreases the rates of remission from depressive disorder when using the CCM model. In view of this knowledge gap, the aim of this study was to identify whether comorbid tobacco use disorder is associated with depression treatment outcomes in the CCM model. Our goal was to measure and compare the treatment adherence and clinical outcomes for depressive symptoms after 6 months of care in a CCM model between smokers and nonsmokers.

We hypothesized that the adjusted odds ratio (AOR) for PDS after 6 months would be higher for smokers, compared to that of nonsmokers, and that the AOR for remission of depressive symptoms after 6 months of care would be lower for smokers compared to nonsmokers in a CCM model. We also hypothesized that current smoking would have a negative impact on treatment adherence within CCM.

Methods

Cohort

This retrospective study was conducted on 5715 patients enrolled in CCM from March 1, 2008, through June 30, 2015, at a large primary care practice with more than 100 000 adult patients at 5 clinical sites in Southeastern Minnesota in the United States. As reviewed previously, CCM consists of a specially trained registered nurse care manager utilizing treatment guidelines, a depression registry, and weekly oversight by a psychiatrist to augment the care of depressed patients.[53,54] Eligibility criteria required that patients be $\geq$18 years of age, have a documented diagnosis of MDD or persistent depressive disorder (dysthymia), and score of an initial Patient Health Questionnaire-9[55] (PHQ-9) score $\geq$10 at the time of enrollment in CCM; the only exclusion criteria for enrollment into CCM was the clinical diagnosis of bipolar disorder. Translation services were utilized for patients who did not speak English.

Exclusion criteria were the following: lack of consent for research authorization for retrospective chart review and incomplete baseline data (including whether smoking status was

Table 1. Comparison of CCM Patients With Depression by Smoker or Nonsmoker Status.

N = 2826	Smokers (n = 727)	Nonsmokers (n = 2099)	*P* Values
Age: median (95% CI)	36.5 (34.9-38.6)	38.9 (37.9-39.7)	.018
Gender: % female (n)	70.0% (509)	78.5% (1647)	<.001
Race: % white (n)	92.7% (674)	93.3% (1958)	.599
Married: % (n)	31.2% (225)	52.3% (1102)	<.001
Diagnosis: % (n)			<.001
First episode	47.7% (347)	52.8% (1,108)	
Recurrent	44.2% (321)	39.9% (838)	
Dysthymia	8.1% (59)	7.3% (153)	
Initial PHQ-9 score: median (95% CI)	16.0 (16.0-17.0)	15.0 (14.0-15.0)	<.001
GAD-7 scores: % (n)			<.001
0-4	7.6% (55)	11.6% (243)	
5-9	17.3% (126)	25.8% (541)	
10-14	32.2% (234)	31.2% (655)	
≥15	42.9% (312)	31.4% (660)	
MDQ negative: % (n)	60.2% (438)	77.8% (1633)	<.001
Treatment adherence at 6 months	60.2% (438)	70.7% (1483)	<.001
Six-month PHQ-9 score of <5	37.9% (166/438)	53.0% (786/1483)	<.001
Six-month PHQ-9 score of <5 (intention to treat)	22.8% (166/727)	37.4% (786/2099)	<.001
Six-month PHQ-9 score of ≥10	36.1% (158/438)	23.6% (339/1438)	<.001
Six-month PHQ-9 score of ≥10 (intention to treat)	21.7% (158/727)	16.2% (339/2099)	<.001

Abbreviations: CCM, collaborative care management; CI, confidence interval; GAD-7, Generalized Anxiety Disorder 7-item scale; MDQ, Mood Disorder Questionnaire; PHQ-9, Patient Health Questionnaire-9.

incomplete). The lack of patient-provided history of cigarette smoking in the electronic medical record (EMR) excluded 1231 patients. Since the goal of the study was to determine the difference between nonsmokers and smokers, those patients who listed their smoking habits as "occasionally" (n = 142) or "quit" (n = 1278; at CCM treatment initiation or after 6 months) were excluded due to the lack of clarity for smoking frequency or length of time since they quit. Finally, 238 patients were excluded from the study due to lack of baseline clinical data. Exclusion criteria were applied, leaving 2826 study participants. Patients were considered enrolled in CCM if they went through the index meeting with the care manager and were not removed from the cohort if they dropped out for any reason.

Data Collection

Baseline demographics, clinical data, and 6-month follow-up PHQ-9 scores were obtained from the CCM enrollment registry. Outcome variables were defined as remission of depressive symptoms with a 6-month follow-up PHQ-9 score of <5, while PDS was defined as a PHQ-9 score of ≥10.[56] Treatment adherence to CCM was determined by whether there was a PHQ-9 score (range: 0-27) documented at 6 months. Active smoking status (smoker/nonsmoker) at enrollment was determined by annually updated patient-provided information stored in the electronic health record. Demographic variables included age, gender, marital status, and race. Clinical predictor variables collected at initial visit included depressive disorders (first episode or recurrent depressive disorder or dysthymia), baseline PHQ-9 score, Generalized Anxiety Disorder-7 (GAD-7, range 0-21)[57] score, and the Mood Disorders Questionnaire (MDQ).[58] An MDQ was scored as negative if the total score was <7 for question 1, question 2 was negative, and question 3 had response of "no problem" or "minor problem."

Statistical analysis was performed using MedCalc software (www.medcalc.org, version 16.4.3). This study was reviewed and approved by our institutional review board. An intention-to-treat analysis was used and those who dropped out of CCM or lacked 6-month PHQ-9 values were assumed to not be in remission and to have PDS. Differences between smokers and nonsmokers were assessed using the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables. Multivariate logistic regression was utilized to examine the association between smoking status and the criterion variables of remission of depressive symptoms, PDS, and CCM treatment adherence, while controlling for baseline differences. Two-tailed *P* values < .05 were considered statistically significant.

Results

Of the 2826 patients in this study, 727 (25.7%) were self-identified as active smokers. As shown in Table 1, among those enrolled in CCM, smokers were more likely to be male, be of younger age, and not married, compared to nonsmokers. Among patients enrolled in CCM at 6 months, those who reported smoking cigarettes demonstrated an increased frequency of recurrent depressive disorder, higher initial PHQ-9 scores, (initial) worse GAD-7 scores, (initial) more abnormal MDQ scores, and were less likely to have a 6-month follow-up PHQ-9 score than nonsmokers. Fewer smokers achieved remission of depressive symptoms and more had PDS at 6 months than nonsmokers.

Multivariate logistic regression analyses were conducted to examine the predictors of remission of depressive symptoms, PDS, and treatment adherence in CCM at 6 months. Figure 1

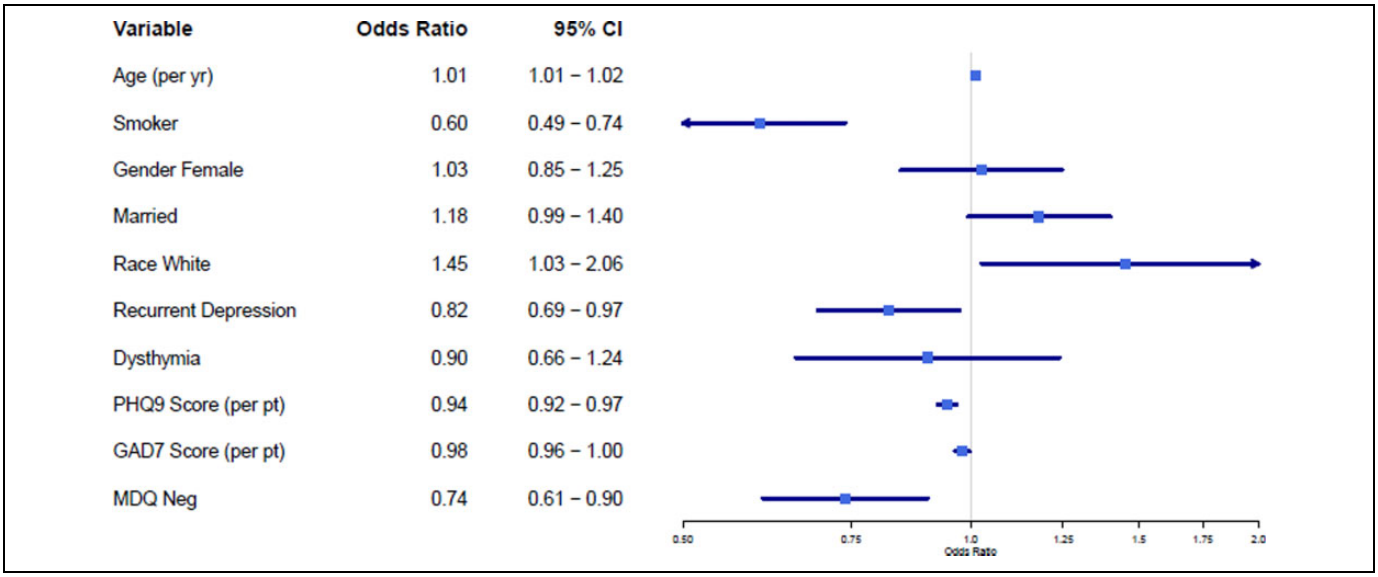

Figure 1. Adjusted odds ratios for remission of depressive symptoms (PHQ-9 of <5) at 6 months after enrollment in collaborative care management for depression, by variable. GAD-7 indicates Generalized Anxiety Disorder 7-item scale; MDQ, Mood Disorder Questionnaire; PHQ-9, Patient Health Questionnaire-9.

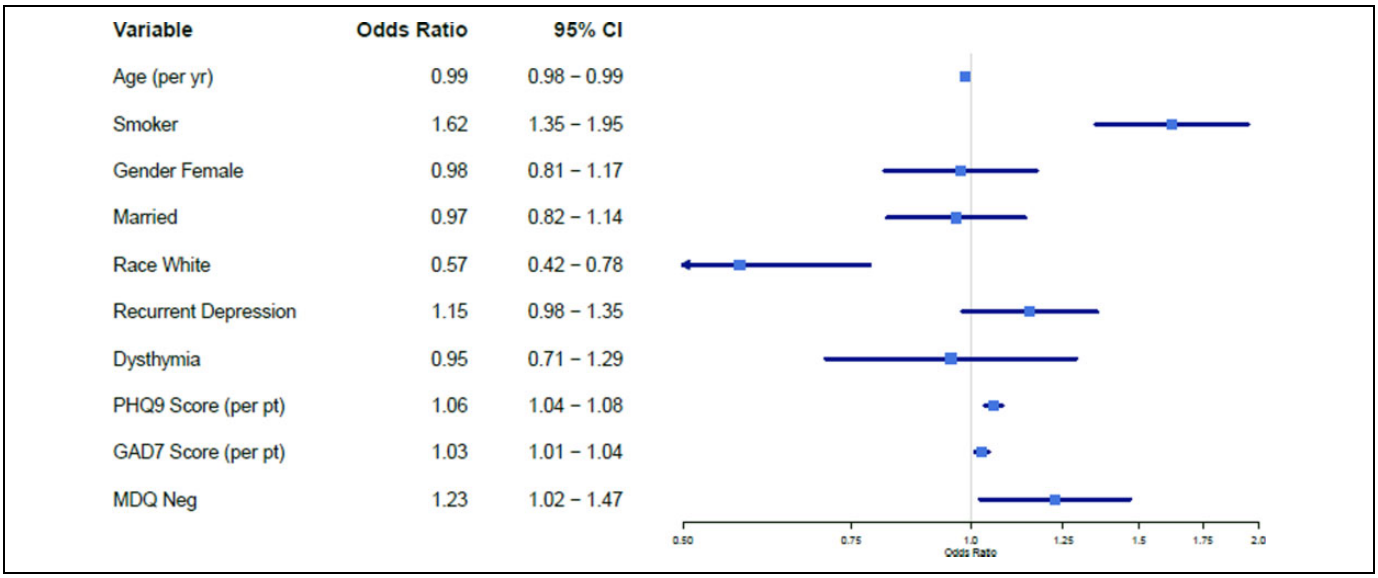

Figure 2. Adjusted odds ratios for persistent depressive symptoms (PHQ-9 of $\geq$10) at 6 months after enrollment in collaborative care management for depression, by variable. GAD-7 indicates Generalized Anxiety Disorder 7-item scale; MDQ, Mood Disorder Questionnaire; PHQ-9, Patient Health Questionnaire-9.

shows the results for remission of depressive symptoms (PHQ-9 < 5) at 6 months, using an intention-to-treat analysis. Smokers were less likely to achieve remission of depressive symptoms compared to nonsmokers (AOR = 0.603, 95% confidence interval [CI]: 0.492-0.739). Smokers with recurrent depressive disorder, higher initial PHQ-9 and GAD-7 scores, and abnormal MDQ screens also had lower odds of achieving remission. Increased age and Caucasian race were also associated with increased adjusted odds of depressive symptom remission at 6 months. Gender, diagnosis of dysthymia, and marital status were not predictive of depression remission. A subgroup analysis of the remeasured patients at 6 months (those adhering to CCM; n = 1921) also demonstrated that smokers were less likely to achieve remission of depressive symptoms than nonsmokers (AOR = 0.662, 95% CI: 0.526-0.833).

Figure 2 shows the results for PDS at 6 months. Smokers were more likely to have PDS at 6 months (AOR = 1.624, 95% CI: 1.353-1.949). Those with higher baseline PHQ-9 and GAD-7 scores and abnormal MDQ screen also had higher odds of PDS at 6 months. Only older age and Caucasian race were associated with lower odds of PDS at 6 months. Gender, clinical diagnosis, and marital status were not predictive of

PDS at 6 months. A subgroup analysis of the remeasured patients at 6 months (those adhering to CCM; n = 1921) also demonstrated that smokers were more likely to have PDS (AOR = 1.547, 95% CI: 1.209-1.980).

Of the patients in this study, 68.0% (n = 1921) adhered with follow-up care at 6 months. In logistic regression modeling for the variable of treatment adherence at 6 months, while adjusting for all other variables, smoking was associated with decreased treatment adherence (AOR = 0.666, 95% CI: 0.553-0.802). Older age (AOR = 1.020, 95% CI: 1.014-1.026) and Caucasian race (AOR = 1.447, 95% CI: 1.069-1.958) were associated with CCM treatment adherence. All other variables were not statistically associated with treatment adherence at 6 months.

Discussion

The results demonstrated that, after 6 months of care in this particular CCM model, patients with comorbid tobacco use disorder and depressive disorders (ie, MDD and persistent depressive disorder) were associated with worse depression treatment outcomes when compared to patients presenting with only depressive disorder. These results are consistent with our hypotheses and prior studies in other clinical settings. We observed that a tobacco use disorder had an increased AOR for PDS at 6 months of 1.624 (95% CI: 1.353-1.949). Furthermore, we observed that having a tobacco use disorder lowered the AOR of depressive symptom remission at 6 months to 0.603 (95% CI: 0.492-0.739). Our results suggest that smokers enrolled in the particular CCM model in this study had statistically significant poorer outcomes for the treatment of depressive disorder compared to nonsmokers.

Within the CCM model, there are likely 2 major reasons for failure to treat patients with depressive disorders and achieve remission: (1) patient nonadherence to a potentially effective treatment plan and/or (2) low efficacy of offered treatment plans for some patient subpopulations within the CCM model. For patients with depressive disorders across all treatment models, there are probably complex causes including environmental, physical health, psychological, neurophysiological, and genetic factors, which differ in causal weight depending on the individual patient and circumstance.

Poor adherence to treatment plans during the measured 6-month period may be one reason to account for the poorer outcomes in the smoker population. We observed that smokers had a significantly low AOR (0.666; 95% CI: 0.553-0.802) for treatment adherence in CCM within 6 months after the initial visit. Other study analyses have focused on behavioral trends in patients who regularly smoke tobacco and identified a higher rate of specialty care utilization for smoker populations, compared to lower rates in nonsmoker populations.[59] These findings suggest that smokers may forgo primary care services and wait to receive medical care in a reactionary fashion, waiting until the emergence of acute morbidity. Addressing this consideration further, other avenues of research have evaluated the impact of smoking status on chronic condition management. These data suggest that smokers have lower medication adherence for chronic conditions.[60,61] These findings would suggest an increased likelihood of smokers not completing courses of pharmacotherapy or behavioral support sessions offered in CCM. Thus, there is reason to believe that among smokers, reduced health literacy, socioeconomic constraints, and poor awareness of the health risks of depressive disorders could have played a role in reduced treatment success.

Furthermore, there is likely a strong set of neuropsychological components operating in the patient population with co-occurring depressive disorder and tobacco use disorder. There is literature to support a bidirectional relationship between nicotine dependence and depressive disorder; depressive disorders can increase the risk of nicotine dependence,[26] while nicotine dependence developing in the absence of depressive symptoms can also increase the risk of developing clinically significant depressive symptoms at a later point.[26,62] It is possible that the use of tobacco and nicotine-containing products is a causal element in the maintenance of depressive features. These findings could support the idea that persistent use of nicotine-containing products might partially account for lower odds of depressive symptom remission and increased odds of PDS after 6 months of care.

Other psychosocial variables unique to smokers could affect the outcomes for the treatment of depressive symptoms, especially when left unaddressed by therapeutic intervention. These include fear of smoking-related health effects, loss in physical function secondary to tobacco-related health problems, financial stress related to the cost of smoking or increased insurance premiums, and feelings of guilt generated by inability to quit despite social pressure to do so. Each of these could impact smokers more than nonsmokers and serve as causal factors in the presence of depressive symptom and reduced treatment success.

Our study does have limitations that largely relate to uncontrolled variables, which could impact depressive symptom scores and treatment success. Although our study did control for mental health disorders captured by the MDQ (bipolar I and II) and GAD-7 (anxiety disorders), our study did not gather data on whether patients had clinically significant attention deficit disorders, which has been a risk factor for tobacco use disorder[63] and depressive disorders[64] in other studies. We did not collect data on other substance use disorders (eg, alcohol[20] or cocaine[19] use disorders) nor did we analyze the presence or absence of chronic pain syndrome, which can all affect mood and alter tobacco use habits.[65] Additionally, the smoker and nonsmoker populations may have differed disproportionately across socioeconomic status (SES), which impacts depressive disorder risk and treatment efficacy. These considerations are particularly important since smoking prevalence is higher among economically disadvantaged groups, and lower SES groups have significantly less successful cessation attempts, lower reported motivation to quit, and reduced social support for quitting.[66] Furthermore, our study did not stratify smokers based on the number of cigarettes smoked per day, which did not allow us to identify whether there was a dose-dependent

response between tobacco use and likelihood of depressive symptom remission after 6 months of care. Despite the presence of these uncontrolled variables, our study methodology simply aimed to measure differences in depressive symptom treatment between 2 populations of patients: those who smoke tobacco regularly compared to those who do not. Further analysis is warranted to identify underlying causes of comorbid tobacco use disorder and depressive disorders.

The study was meant to provide a foundation for further research on treatment outcomes for patients with comorbid depressive disorder and tobacco use disorder. The ultimate clinical goal should be to tailor the CCM approach to specific subpopulations of people (eg, patients with tobacco use disorder) within the population of patients reporting to primary care with depressive disorder. Patients with comorbid mental health and tobacco use disorders are good candidates for smoking cessation intervention[67] and have increased likelihood of quitting smoking compared to individuals not receiving mental health treatment.[68] Future research and clinical pilots could explore using smoking cessation treatment in combination with CCM depressive disorder management. Combined smoking cessation and depressive disorder management should tailor psychosocial support,[69] management of changes in mood during smoking cessation intervention,[70] and tapered nicotine replacement therapy or bupropion pharmacotherapy.[71,72] Being able to accurately assess and treat the population of patients who present with both depressive disorders and tobacco use disorders has potential import for improving their quality of life, reducing comorbidities, and reducing health-care costs.

Conclusion

Depressive disorders and tobacco use disorder are 2 of the most common disorders treated in primary care practices, and both have a significant impact on the health and well-being of patients. When tobacco use disorder and depression are present concurrently in the same patient, the impact may be multiplied and the successful treatment of either disorder may become more complicated.

Our research revealed that self-identified tobacco use was associated with decreased adherence and effectiveness in treating patients with comorbid depressive disorders and tobacco use disorder compared to patients who present with only a depressive disorder. These results should prompt further studies on how the CCM model could be adapted and whether tailored psychosocial and pharmacotherapeutic smoking cessation interventions affect depressive disorder outcomes.

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Declaration of Conflicting Interests

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