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Review
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Review

Exploring Issues of Comorbid Conditions in People Who Smoke

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Abstract

Smoking affects comorbid disease outcomes, and patients with comorbid conditions may have unique characteristics that are important to consider when treating tobacco use. However, addressing tobacco in patients being treated for comorbid conditions is not a consistent practice. Recognizing the need for a "call-to-action" to address tobacco use in people with comorbid conditions, the Tobacco Treatment Network within the Society for Research on Nicotine and Tobacco (SRNT) convened a Comorbidities Workgroup to explore the relationship between smoking and comorbid disease to identify common themes including: the harms associated with continued tobacco use, the frequency of comorbid disease and tobacco use, the potential effect of comorbid disease on the ability to quit tobacco use, the association between tobacco use and suboptimal disease-specific treatment response, and evidence regarding potential approaches to improve addressing tobacco use in patients with comorbid disease. Five candidate conditions (psychiatric, cancer, cardiovascular, pulmonary, and human immunodeficiency virus infected patients) were explored. Across comorbid conditions, smoking adversely affects treatment efficacy and promotes other adverse health conditions. People with comorbid conditions who smoke are motivated to quit and respond to evidence-based smoking cessation treatments. However, tobacco cessation is not regularly incorporated into the clinical care of many individuals with comorbidities. Optimal strategies for addressing tobacco use within each comorbid disease are also not well defined. Further work is needed to disseminate evidence-based care into clinical practice for smokers with comorbid disease and addiction research should consider comorbid conditions as an important construct to explore.

Implications: This article explores how physical and psychiatric conditions may interact in the treatment of tobacco dependence, and discusses the need for smoking cessation as a critical component of comorbid condition management. Five common comorbid domains—psychiatric, cancer, pulmonary, cardiovascular, and human immunodeficiency virus (HIV)—are highlighted to illustrate how these different conditions might interact with smoking with respect to prevalence and harm, motivation to quit, and cessation treatment utilization and success.

Introduction

The global prevalence of smoking decreased from 51.8% in 1980 to 37.3% in 2012, and in the United States, adult smoking prevalence has declined to 17.8%.[1] This is largely due to the development of successful policy, prevention, and treatment interventions.[2] However, to continue this progress, tobacco intervention science will have to continue to evolve. One issue that needs to be addressed is that the traditional clinical approach for the "typical" person who smokes does not take into consideration potential comorbid conditions that may be caused by smoking and may interact with smoking cessation efforts.

The emergence of a more holistic approach to care illustrates the need for clinicians and researchers to view people who smoke as integrated entities rather than as sets of discrete diagnoses. What do we know about how smoking affects comorbid disease outcomes? Do patients with comorbid conditions have unique characteristics that are important to consider when facilitating tobacco cessation? Examining potential clinical and biological mechanisms by which a specific condition may influence smoking could allow a clinician or researcher to examine the overall picture. For example, a patient who smokes may present with a psychiatric condition (eg, depression) that is exacerbated by a cancer diagnosis. Both comorbid conditions may affect motivation to quit as well as smoking cessation efficacy, and conversely, smoking may impact treatment for both cancer and depression.[3–5] Understanding how cancer may motivate cessation but cancer-related depression may reduce self-efficacy and response to rewards may help guide the clinician in how to best facilitate effective cessation treatment.

Treatment for comorbid conditions (eg, cancer and smoking) can be applied using sequential, parallel, or integrated approaches. Sequential approaches involve completion or stabilization of one condition before treatment of the second condition can be started.[6] Typically, little interaction occurs between providers in the context of sequential treatment. Parallel approaches involve treating the disorders simultaneously, ideally with collaboration between the providers on the treatment plan.[6] However, collaboration does not necessarily happen in a parallel practice, such as when one medical provider is not integrated into the same healthcare system as another medical provider who is treating the comorbid condition. Thus, a focus on the condition interactions is not necessarily a hallmark of either parallel or sequential treatment approaches. In integrated treatment both conditions are treated as "primary" by the same team and the providers work in concert to deliver a consistent treatment plan.[6] The studies discussed in this article utilize each of these different treatment approaches. However, we will make the case that treatment of smoking and a comorbid condition should utilize a treatment plan that focuses on condition interactions.

Part of the condition interaction is that smoking is often associated with stigmatization in patients with comorbid diseases.[7–9] Patients may feel guilt associated with a smoking-related condition and may misreport tobacco use due to stigmatization or other feelings (eg, shame).[10,11] This is an important element of the smoking-comorbid condition interaction that needs to be understood by both researchers and practitioners. For the purposes of this manuscript, we have attempted to reduce the stigma associated with smoking and support a more holistic approach by referring to "individuals who smoke" or "patients who smoke" rather than referring to people as "smokers." In other words, tobacco dependence is just one component of an individual's health behaviors and diagnoses.

Recognizing the deficits in addressing tobacco use in people with comorbid disease, the Tobacco Treatment Network within the Society for Research on Nicotine and Tobacco (SRNT) convened a Comorbidities Workgroup to explore the relationship between smoking and comorbid disease. The purpose of this article is to explore how physical and psychiatric conditions may interact in the treatment of tobacco dependence, and to discuss the need for smoking cessation as a critical component of comorbid condition management (Table 1). This article is not intended to be a comprehensive review of the literature regarding co-occurring conditions, but rather a synthesis of these data with the goal of understanding how these conditions interact with smoking. To that end, reviews and meta-analyses are cited where possible. This article will discuss: (1) the frequency of multiple diagnoses among individuals who consume tobacco, (2) the potential impact of various conditions on the ability to quit tobacco use, (3) prevalence and harm in continuing to smoke in each comorbid condition population, (4) the association between tobacco use by individuals with comorbid conditions and suboptimal treatment response and/or health outcomes, and (5) the evidence regarding potential approaches to improve clinical practice and suggestions for future clinical research for tobacco cessation. This article is not intended to be an exhaustive review of all possible co-occurring

Table 1. Common Themes of Addressing Tobacco Use in People With Comorbid Conditions

Smoking is associated with poor therapeutic outcomes in patients with comorbid disease
Continued smoking increases the risk for developing additional adverse health conditions after diagnosis and/or treatment of a comorbid condition
Tobacco assessment and cessation support is not well incorporated into clinical care and research for comorbid disease
People with comorbid conditions appear to have similar or improved motivation to quit. The "teachable moment" may be useful to improve motivation to quit
Multiple comorbid conditions (psychiatric, cancer, etc.) may occur within a patient who uses tobacco and may be important components of developing individualized care
Smoking cessation medications may interact with medications used to treat comorbid conditions
Evidence-based approaches to tobacco cessation (counseling and pharmacotherapy) can be used across comorbid conditions
All people who use tobacco, with or without a comorbid condition, should receive evidence-based tobacco cessation support

disorders. Rather, five common comorbid domains—psychiatric, cancer, pulmonary, cardiovascular, and human immunodeficiency virus (HIV)—will be highlighted to illustrate how these different conditions might interact with smoking with respect to prevalence and harm, motivation to quit, and cessation treatment utilization and success. Discussion will further emphasize a better understanding of how to integrate smoking and comorbid disease treatment, and to promote the treatment of tobacco dependence for patients with these comorbid conditions. It should be noted that this article focuses on smoking combustible cigarettes, as that is the most common form of tobacco use and provides the basis for most of the extant literature.

Psychiatric Comorbidities

Prevalence and Harm

Individuals who smoke are more likely to have psychiatric comorbidities than those who don't smoke, and individuals with psychiatric comorbidities are more likely to smoke than people without such diagnoses.[12–26] For some psychiatric diagnoses such as schizophrenia and substance abuse, smoking rates are four times greater than in the general population.[27–29] Current smoking and nicotine dependence are also related to personality disorders; they have strong positive associations with antisocial, dependent, schizotypal, borderline, and narcissistic personality disorders, but negative associations with avoidant and schizoid personality disorder, and mixed results with obsessive-compulsive personality disorder.[13,14,30] In addition to higher smoking rates, individuals with psychiatric comorbidities who smoke are more likely to suffer negative health consequences due to their smoking.[17,19] The high rates of smoking, higher levels of dependence, and disparate harms from smoking all suggest that smoking among individuals with psychiatric comorbidities needs to be comprehensively addressed, including providing evidence-based treatment.[2]

Addressing Tobacco Use

Some research suggests that individuals with psychiatric comorbidities, such as depression[31] or bipolar disorder,[32] who smoke are less likely to make a quit attempt. However, other evidence suggests that these people are as motivated to quit smoking as people without psychiatric comorbidities,[33–37] and do make quit attempts.[38,39]

There are at least three issues that may impair smoking cessation motivation among individuals with psychiatric comorbidities. One issue is fear of worsening mental health or drug relapse after quitting. Both clinicians and people who smoke have suggested that smoking cessation might remove an important affective coping strategy and may exacerbate mental illness or jeopardize sobriety from other addictive substances[40–46]; there is mixed evidence regarding this concern. Whereas some data suggest that cessation may exacerbate the symptoms of depression[47,48] and/or schizophrenia,[49] other studies have shown that quitting smoking improved mental health, including reduced depression, anxiety, stress, improved mood and quality of life,[50] and increased abstinence from illicit drugs and alcohol.[34,51–55] A second issue in individuals with mental illness and addiction is that they often have treatment environments that support continued smoking (eg, "smoke breaks" during treatment groups), use smoking to facilitate social interaction, and have social networks that include other people who smoke, reducing support for cessation activities.[56,57] Finally, motivation may also be hampered by a lack of knowledge. Several studies have found that people with mental illness who smoke have less understanding of the health risks of smoking, the benefits of quitting, and cessation treatment resources.[56,57]

There are several symptom-specific issues that may impair cessation motivation or success. For instance, certain psychiatric disorders (eg, borderline personality disorder, drug dependence, schizophrenia) associated with lack of coping skills, poor distress tolerance, and emotion dysregulation are associated with decreased smoking cessation motivation and success.[58–65] Alternatively, obsessive-compulsive disorder is associated with low impulsivity and risk taking which could bolster smoking cessation success.[66,67] Therefore, underlying traits or symptoms of specific psychiatric comorbidities may influence cessation motivation and success, not necessarily a diagnosis of mental illness. Research is needed to address whether specific components of mental illness may influence cessation motivation, rather than focusing exclusively on specific diagnoses as a single entity.

Unlike the general population, the smoking rate among people with mental illness has not declined over time.[68] This may be due to less motivation to quit and fewer quit attempts, or lower cessation success. Indeed, some diagnoses are linked with reduced cessation success (eg, anxiety/posttraumatic stress disorder,[39] depression,[69] borderline, antisocial, and avoidant personality disorder[70]) with recent or current psychiatric symptoms increasing risk.[25,71–77] However, from a population-based perspective, lower cessation rates among individuals with mental illness who smoke may be related to access to treatment. Clinicians who treat patients with mental illness rarely provide smoking cessation interventions.[78–80] This is despite the fact that training behavioral health professionals to implement tobacco dependence treatment can increase provision of smoking cessation treatment and quit attempts among people with mental illness, making it an ideal situation for integrated treatment.[81] Further, when individuals with psychiatric comorbidities do receive evidence-based cessation treatments, some individuals respond to evidence-based medications including varenicline (depression[82]; schizophrenia[83,84]), bupropion (past depression only[85]; schizophrenia[84,86]), bupropion + nicotine replacement therapy (NRT) (schizophrenia[27,84,87]) while others are less responsive to evidence-based medications (anxiety[53]; substance use disorders[34]) or more likely to drop out of smoking cessation treatment early (personality disorders[88]). Evidence-based strategies for adapting specific medications and treatments in select populations with mental illness are not well defined.

While patients with mental illness may respond to evidence-based cessation treatment, they may not quit at the same rates as those without a psychiatric comorbidity. Patients with mental illness may need tailored smoking cessation treatment to address this comorbidity. Research suggests that for some diagnoses, like posttraumatic stress disorder, integrating smoking cessation into mental health care increases abstinence rates.[89,90] Also, psychosocial mood management with standard cessation treatment has enhanced cessation rates for patients with current and past depression.[85,91] Data also indicate that patients with mental illness who smoke and received treatment for their mental illness within the last year were more likely to quit.[68] This suggests that mental health and smoking cessation may need to be treated simultaneously. This is consistent with substance use treatment research which shows that concurrent treatment for nontobacco substance use disorder and tobacco dependence enhances abstinence from both tobacco and other substances.[34,92–97]

Cancer Comorbidities

Prevalence and Harm

Well-established evidence demonstrates that tobacco causes at least 17 types of cancers.[98] According to the 2014 Surgeon General's

Report, the evidence is sufficient to infer a causal relationship between continued cigarette smoking and adverse health outcomes. Cigarette smoking results in increased all-cause mortality by a median of 51% and cancer-specific mortality by a median of 61%. In contrast, former smoking has a lesser median risk of 22% for overall mortality and no significant effect (3%) for cancer specific mortality. Smoking is also causally related to increased risk for second primary cancers and is associated with an increased risk of recurrence, poorer response to treatment, and increased treatment-related toxicity. The adverse effects of smoking span virtually all cancer disease sites and all cancer treatment modalities (surgery, radiotherapy, and chemotherapy). Based on these findings, the commitment of resources to provide tobacco cessation activities for all cancer patients as a clinical standard of care is well justified.[99]

Several recent reviews have discussed the need and methods to address smoking in cancer patients[3–5,100,101]; however, no clear definitions exist.[5,102–104] For example, current smoking in the cancer literature has been defined as same day use as well as within the past day, week, month, year, or even 5 years. Current tobacco use has also been defined as only people who smoke at least 1, 10, or 20 cigarettes per day. These definitions are not standard, confound attempts to analyze the effects of smoking on cancer treatment outcomes, and make it difficult for clinical oncologists to understand which cancer patients require tobacco cessation support and assistance. At the time of this publication, no guidelines by any national cancer organization explicitly define tobacco use in cancer patients.

The Surgeon General's Report concludes that quitting smoking improves cancer treatment outcomes, but this is based primarily on the fact that current smoking adversely affects cancer treatment while former smoking has a lesser or no adverse effect.[98] Several studies demonstrate that quitting smoking after a cancer diagnosis improved outcomes, including reduced risk of developing a second primary cancer[105,106] and reduced treatment toxicity.[107–109] A study in 205 head/neck cancer patients demonstrated that 43% of currently smoking patients treated with radiotherapy in the morning had higher treatment toxicity as compared with 72% of smoking patients treated with radiotherapy in the afternoon.[109] This may be due to reduced smoking among patients treated in the morning compared to patients treated in the afternoon who continue daily smoking which, in turn, supports a potential acutely reversible benefit of smoking cessation. Given the adverse effects of tobacco on clinical cancer outcomes,[98] smoking cessation in cancer patients is an urgent priority to potentially prevent the adverse effects of tobacco on cancer treatment response.[4,5,100] A rationale may even exist to delay non-urgent cancer treatment until smoking cessation has occurred in order to optimize cancer treatment response. However, these questions require well-designed clinical trials to identify the potential dose and time dependent effects of smoking and smoking cessation on clinical cancer treatment outcomes.

Addressing Tobacco Use

The "teachable moment" is highly relevant to cancer patients.[4,5,100,110] Patients diagnosed with cancer have a life-changing diagnosis and are often motivated to change health behaviors to improve their cancer outcomes. Several studies have identified factors associated with motivation to stop smoking in cancer patients. In a recent survey of 105 survivors of tobacco-related cancers who smoked at the time of diagnosis, positive influences for cessation included physician advice, social influence, and the diagnosis of cancer itself.[111] High motivation to quit and lower perceived adverse effects associated with quitting also increase quit rates.[112] A cancer diagnosis in a family member also motivates cessation efforts in non-cancer patients.[113] In contrast, addiction, stress, feeling hopeless, lower readiness or motivation to quit, lower self-confidence in being able to quit alone, and lower smoking rates are significant barriers to cessation[111,114] A matched case-control study of lung cancer patients who smoke and non-lung cancer patients demonstrated that lung cancer patients are more motivated to quit and have higher 6-month quit rates.[115] However, adjustment for other demographics and tobacco use parameters eliminates differences between lung cancer patients and the general population, indirectly suggesting that common motivation exists between cancer patients and non-cancer patients.

Though addressing tobacco use in all cancer patients is recommended by the American Society for Clinical Oncology,[116] the American Association for Cancer Research,[101] and other cancer organizations, many cancer patients lack adequate cessation support. Surveys of oncologists consistently demonstrate that approximately 90% of oncologists ask patients about tobacco use and 80% advise patients to quit smoking, but less than half of oncologists regularly provide tobacco cessation support.[117,118] Remarkably, both surveys demonstrated that approximately 90% of respondents felt that smoking adversely affected patient outcomes and approximately 80% thought smoking cessation should be a standard part of cancer care. Thus, even motivated oncologists do not regularly provide cessation support. Lack of interest by cancer patients to stop smoking was a dominant perceived barrier[117–119]; however, this perception has been challenged. Head and neck cancer patients who were more confident in quitting actually participated less in a cessation program while patients who felt it was difficult to quit had a higher rate of participating in a structured cessation intervention.[120] In an "opt out" study of over 2700 cancer patients who smoked who were screened with mandatory structured tobacco assessments, automatically referred to a dedicated cessation program, and proactively contacted by a dedicated cessation specialist, over 90% of patients contacted were receptive to participating in a phone based cessation program.[121] This study suggests that removing clinician bias from referral of cancer patients to cessation support programs may substantially improve access to cessation support and patient receptiveness.

In the general population, more intensive tobacco cessation counseling improves quit rates.[2] However, few data support that more intensive cessation interventions improve quit rates in cancer patients[3–5,100] In a trial of 186 head/neck cancer patients, there was no significant difference in quit rates between patients offered minimal advice compared to an enhanced intervention, using trained clinicians, perhaps because quit rates were very high with 65%–70% continuous abstinence at 1-year follow-up.[122] A later study also suggested no significant improvement in cessation rates in cancer patients offered health advice with or without cognitive behavioral treatment.[112] In a large randomized trial of 432 cancer patients, brief physician-delivered intervention (cessation advice, optional NRT, and written materials) was not significantly better than usual care (unstructured advice from physicians), with relatively low 12–15% abstinence rates at 6–12 months,[123] though patients with head/neck or lung cancer had superior quit rates compared patients with nontobacco related cancers. More intensive cessation programs should result in higher quit rates, but may inherently treat fewer patients per cessation specialist.[100] Cancer patients are burdened with intensive treatment regimens commonly associated with aggressive clinical follow-up and a broad spectrum of potential cancer treatment toxicities. Therefore, cancer patients and oncologists may be reluctant

to develop and support an intensive tobacco cessation approach in a resource-limited environment. However, such programs can be mutually beneficial to oncologists and patients in terms of delivering specialized treatment and optimizing communication among providers and between providers and patients.[119]

The method of cessation support should consider not only cessation efficacy, but also ability to disseminate cessation support services to cancer patient cohorts in a busy clinical setting. Automated assessment and referral programs may be highly effective.[121] On the other hand, patients should have access to individualized and appropriately intensive tobacco cessation interventions where available.[100,124] For example, cancer patients often take multiple medications that may interact with cessation medications and modifications may be needed, such as potentially modifying tamoxifen dose if bupropion is prescribed. Designing effective, integrated cessation strategies for research or clinical practice will require careful consideration and increased participation from both tobacco cessation experts as well as clinical oncology providers.

Pulmonary Comorbidities

Prevalence and Harm

Cigarette smoking is the dominant cause of chronic obstructive pulmonary disease (COPD) in men and women in the United States.[98] Prevalence of moderate or worse COPD was 13.5% during 1988 to 1994 and COPD mortality has increased between 1979 and 2007. Further, smoking causes acute exacerbations of asthma in adults, an increased risk of *Mycobacterium Tuberculosis* (TB) infection, and increased mortality due to TB.[98] Meta-analyses of the association between smoking and mortality from active TB showed a strong, positive dose response relationship between smoking and mortality with relative risks of approximately 2. Similarly, dose-response relationships have been observed for progression to active TB disease in patients with latent TB who smoke.

Studies have shown that smoking cessation improves pulmonary function and decreases normal age-related decline in the forced expiratory volume at 1 second (FEV_1). In a study from 10 North American medical centers of 3926 patients with mild COPD who smoked[125] and where pulmonary function was measured annually for 5 years, subjects who quit smoking experienced a 2% improvement in FEV_1 in the year after quitting. Quitters had a rate of decline of FEV_1 that was comparable to patients who never smoked and half that of patients who continued to smoke. Similarly, 11-year follow-up of a randomized smoking cessation trial with regular bronchodilator use in 5887 middle aged patients with impaired airway obstruction showed that men who quit at the beginning of the trial had a decreased rate of FEV_1 decline compared to patients who continued to smoke.[126,127] Among patients who continued to smoke, 38% had an FEV_1 less than 60% of the normal predicted value, compared to only 10% of sustained quitters. A follow-up of these patients noted improved all-cause mortality compared to usual care (8.83 per 1000 person-years vs. 10.38 per 1000 person-years; P = .03).[128] Thus, smoking cessation reduces decline in pulmonary function.

Addressing Tobacco Use

In a survey study of 4035 individuals who smoke, people with COPD were equally likely to want to quit smoking compared to healthy individuals.[129] Similar to their healthy counterparts, 73% of COPD respondents reported their reason for wanting to quit was that smoking "damages health." Other reasons for quitting included potential damage to health of self or others, self-affirmation, poor example to children, and economic considerations. Furthermore, there were no significant differences between those with COPD and healthy people with respect to the phase of smoking cessation (49.7% precontemplative, 13.1% contemplative, and 9.2% preparation). Importantly, the study observed that people with COPD who smoke are more highly nicotine dependent and smoke more cigarettes per day than healthy people who smoke. These data suggest that people with COPD may be equally motivated to quit smoking but may require more intensive pharmacotherapy regimens to achieve abstinence compared to people without COPD.

The concept of "lung age" has shown promise in motivating people with chronic lung disease to stop smoking.[130,131] Lung age is defined as the age of the average person who has an FEV_1 equal to that of the individual. Since people who smoke experience a more rapid decline in FEV_1 than people who do not smoke, lung age in a patient who smokes will be higher than his or her chronologic age. In a multicenter trial where patients who smoked were randomized according to lung age versus pulmonary function and provided advice to quit smoking with access to local cessation resources, those randomized to the lung age group had a significantly higher quit rate at 12 months compared to the FEV_1 raw number group (13.6% vs. 6.4%, P = .005). The mechanism by which this effect occurred was not entirely clear, since subjects with worse lung age were no more likely to quit than subjects with normal lung age in either group. A more recent meta-analysis of 15 clinical trials studied the efficacy of providing additional biomarkers, such as pulmonary function, to motivate individuals to quit smoking.[132] There was no evidence that CO level, spirometry, or genetic susceptibility to lung cancer increased smoking cessation rates.

Both behavioral and pharmacologic treatments for smoking cessation are effective for patients with chronic lung diseases. In randomized trials, both bupropion and varenicline have been shown to increase quit rates as compared with placebo.[133,134] Combining behavioral counseling and pharmacotherapy in COPD patients have also shown positive results. In the Lung Health Study,[135,136] patients with early COPD were randomized to one of three groups: usual care (no intervention), intensive smoking intervention (counseling and nicotine gum) and inhaled bronchodilator, and intensive smoking intervention with inhaled placebo. Point prevalence at 12 months and prolonged abstinence after 5 years were significantly higher in the groups receiving the smoking cessation intervention compared to usual care (point prevalence abstinence at 12 months: relative risk [RR] 3.85, confidence interval [CI]: 3.30–4.48; prolonged abstinence after 5 years: *RR* 4.01, CI:3.25–4.93) and were similar regardless of whether bronchodilators were given. A smaller randomized controlled trial involving 370 COPD patients evaluated the efficacy of nicotine sublingual tablets or placebo combined with either low or high levels of behavioral support for smoking cessation provided by nurses. Smoking cessation rates as measured by 6-month point prevalence abstinence were significantly greater in the sublingual nicotine group as compared to placebo (23% vs. 10%, *OR* 3.46, CI: 1.58–5.2), while there were no significant differences between those receiving more or less behavioral support.[137] These studies suggest that some evidence-based strategies in the general population may apply to management of patients with COPD.

Cardiovascular Comorbidities

Prevalence and Harm

Smoking is a risk factor for cardiovascular disease (CVD; including myocardial infarction [MI], stroke, and atherosclerosis), and

approximately 151 000 people aged 35 years and older die each year from smoking-related CVD.[138] Research has shown that patients who smoke have increased levels of inflammatory and haemostatic makers, such as C-reactive protein, white cell count, and fibrinogen, all independent risk factors for coronary heart disease.[139] Smoking increases the risk of adverse events after surgical procedures for CVD. For example, an analysis of the effect of smoking on outcomes of percutaneous coronary revascularization revealed that patients who continued to smoke after successful percutaneous coronary revascularization were at greater risk for Q-wave infarction (*RR* 2.08, CI 1.16–3.72]) and death (*RR* 1.76, CI 1.37–2.26]) compared to patients who did not smoke.[140] Research also estimates a 36% reduction in crude relative risk of mortality for patients who quit compared to those who keep smoking.[141]

Addressing Tobacco Use

A suspected or significant cardiac event (eg, MI) or surgery presents a "teachable moment" to motivate cessation. Whether the teachable moment translates to cessation may be a matter of the type of intervention required to treat the disease. For example, patients who smoked who presented for treatment for peripheral arterial disease and received an open revascularization procedures had an 8.26-fold higher odds of quitting or cutting down by 50% compared to those who had undergone percutaneous interventions (95% CI 1.18–76.67).[142] Even though the patients viewed their smoking as contributing to their disease (94%), and a majority reported that the medical procedure itself was life-changing, only those who had the more invasive procedure quit or reduced their smoking. These results lend credence to the theory that level of motivation to quit smoking may depend on the type of the procedure, or the length of the hospital stay (with fewer opportunities to smoke), as opposed to a CVD diagnosis per se.

Instead of promoting cessation, some comorbid medical conditions associated with CVD may motivate patients to continue smoking. For example, the current smoking prevalence among those with depression and anxiety is 36% and up to 46%, respectively.[15] Depression and anxiety are associated with an elevated risk of CVD[143,144] and incident acute MI.[145] In parallel with the section on psychiatric comorbidity, patients who smoke and who present for CVD treatment may need to also be evaluated for depression, stress, and anxiety, as these variables may interfere with quit attempts.

Patients with CVD would reduce their risk of complications and mortality if they quit smoking. Rates of cessation using most approved smoking cessation interventions are similar to the general population. With respect to behavioral smoking cessation interventions, research has shown that even brief inpatient counseling and telephone follow-up increases smoking abstinence 1 year after discharge in patients post-MI.[146] First-line pharmacological interventions (ie, NRT, bupropion, and varenicline) have also been evaluated in CVD patients. Several trials have evaluated the safety of NRT for those with a history of CVD, and no differences were found in the rate of cardiovascular events between patients treated with NRT versus placebo.[147–149] However, due to lack of research among particular subgroups, the current clinical practice guidelines recommend that NRT be used with caution in patients who have had recent (within 2 weeks) MI, and those with serious arrhythmias or unstable angina pectoris.[2] Importantly, the safety profile of bupropion sustained release in patients with CVD was similar to that previously observed in the general population.[150] With respect to varenicline, prior research had suggested that varenicline was associated with an increased risk of cardiovascular events.[151] However, a recent review and meta-analysis found that this drug was not associated with risk of serious adverse cardiovascular events compared to placebo.[152] Varenicline carries a caution label for use in patients with CVD, but may still be a viable treatment option based on available data.

The American Heart Association (AHA)/American College of Cardiology (ACC) recommends complete cessation and no exposure to environmental tobacco smoke as a risk-reduction therapy for patients with CVD and other atherosclerotic vascular disease.[153] However, reported rates of physician intervention are less than ideal. For example, in a study of inpatient smoking-cessation counseling in patients with acute MI, only 52.1% of 3511 patients reporting current smoking were offered cessation counseling, and cardiologists were less likely to offer smoking cessation advice than family physicians.[154] However, the benefits of smoking cessation for cardiac patients are clear. Patients who received smoking cessation counseling had a 37% lower risk of mortality than those not counseled post-MI.[154] Further, smoking cessation after coronary artery bypass graft surgery independently predicted a lower risk of death and coronary reintervention during a 20-year follow-up compared to patients who continued smoking.[155] Cardiovascular patients would benefit from dedicated smoking cessation interventions to help lower the risk of CVD, surgical complications, and death.

HIV Comorbidities

Prevalence and Harm

Smoking prevalence among people infected with HIV is two to four times higher than the general population.[156–166] HIV-infected individuals smoke a greater number of cigarettes per day, are more nicotine dependent, and are less successful at quitting.[158,163,166] People with HIV are more likely to suffer the adverse health consequences of smoking such as cancer, CVD, and respiratory disease.[166–170] Although some research has found no relationship between current smoking and HIV disease progression,[171,172] other studies have found that smoking is associated with increased immunologic failure and mortality in HIV-infected individuals.[169,170,173,174] According to a population-based cohort study, HIV-infected patients lose more years of life to smoking than to HIV-related causes.[175] Cigarette smoking among HIV-infected individuals is negatively associated with antiretroviral adherence, antiretroviral response, quality of life, and social support,[161,169,173,176,177] and positively associated with substance use, depression, and HIV-related symptoms.[156,158–162,178,179] Though treatment advances for HIV have led to significant improvements in longevity, the significant adverse effects of smoking in this population require attention.

Addressing Tobacco Use

Among HIV-infected patients, smoking cessation reduces HIV-symptom burden, CVD risk, and bacterial pneumonia.[167,180–182] Most HIV-infected patients who smoke are motivated to quit and have made a quit attempt during their lifetime.[157,179] A longitudinal study of people with HIV found that 33% of 2223 HIV-infected patients who smoke made at least one quit attempt over a 5-year period.[183] However, another longitudinal study found that, among the 26% of 4833 HIV-infected patients who quit smoking, 48% relapsed back to smoking.[184] Among HIV-infected patients who smoke, several studies have found that motivation for quitting and quit attempts are negatively related to illicit drug use and emotional distress.[160,163,183]

In HIV-infected individuals, smoking cessation is positively associated with age and duration of known HIV status, and improves HIV symptom burden.[180,183] A qualitative study of HIV-infected patients who reported current or former smoking found that participants were uneducated about the effect of their smoking on their health and used smoking as a source of comfort in their "battle" with HIV.[185] Further, 43% of HIV-infected patients who smoke have social networks that include other people who smoke, and these social networks likely impact smoking cessation motivation and success.[186] Although many HIV-infected patients are motivated to quit and cessation improves health, these patients face many barriers to cessation that likely need to be addressed to improve motivation for quitting, quit attempts, and cessation success.

Research on smoking cessation interventions among HIV-infected patients is still in its infancy.[187] While several pilot, small scale, and nonrandomized trials of smoking cessation interventions have been conducted in this population,[188–192] only a few large randomized controlled trials have been published with variable quit rates. An open label pilot study of varenicline among HIV-infected patients had quit rates (42% continuous abstinence from weeks 9 to 12) and adverse event rates similar to the general population.[193] In a randomized trial of individual counseling plus NRT, an internet intervention plus NRT, or self-help plus NRT among 209 HIV-infected patients found no significant differences in post-treatment 7-day abstinence (24%, 26%, 29%, respectively) between the treatment groups.[194] Vidrine and colleagues compared usual care (self-help materials, brief advice, and instructions on how to receive nicotine patches at the clinic) to usual care plus cellular phone based counseling among 474 HIV-infected patients, and found significantly greater 7-day abstinence among those who received the cellular phone intervention (12%) as compared to those who received usual care (3%) at 3-month follow-up.[195] Assessing the overall treatment effect (7-day abstinence outcomes from 3-, 6- and 12-month follow-ups), participants in the cellular phone intervention group were 2.41 times ($P = .049$) more likely to be quit than those in the usual care group.[196] However, the treatment effect, which was strongest at 3 months ($OR = 4.3$, $P < .001$), diminished over time ($P > .05$ at later follow-ups). Another study compared a brief standard of care intervention and NRT to a more intensive motivational intervention plus NRT among 444 HIV-infected patients and found 7-day post-treatment abstinence rates of 12% and 13%, respectively.[197] In concert with the discussion on psychiatric comorbidities, researchers have found that improvements in depression, anxiety, decisional balance, and self-efficacy mediate the relationships between smoking cessation treatment and smoking abstinence in HIV-infected patients.[198,199] Further research is needed to optimize smoking cessation treatment efficacy for this population.

Discussion

Through this discussion of five different comorbid domains, it is clear that each domain has a different relation to smoking, making the need to consider comorbid conditions in people who smoke quite evident. However, the data also suggest that people who smoke want to quit, regardless of their different comorbid conditions. Though there may be a broad variety of issues that differ among people with one or more comorbid conditions, there are several common themes that can be used to discuss tobacco use and the need to quit smoking. Perhaps most significantly, smoking may adversely affect the treatment efficacy for comorbid conditions and smoking invariably continues to promote a host of other adverse health conditions. Case scenarios in HIV[175] and prostate cancer[200] patients suggest that smoking-related health conditions may dominate overall mortality patterns to a greater extent than the comorbid condition itself.

Across comorbid medical conditions, it is important to consider the impact of psychiatric comorbidities on motivation to quit, treatment response, and ability to successfully quit smoking. For instance, individuals with psychiatric comorbidities may use tobacco to manage their psychiatric symptoms, thereby reducing their motivation to quit. Conversely, patients may be more receptive to smoking cessation when diagnosed with a new medical condition, thus providing a "teachable moment." Such a moment can only be capitalized upon if there are accurate tobacco use assessments in place, as well as a way to guide individuals who smoke to treatment and limit potential barriers related to cessation efficacy.

The adverse effects of continued smoking on medical treatment outcomes require that we advocate for smoking cessation as a standard of clinical care for all patients.[2] Patients should be screened with standardized tobacco use assessments, and optional biochemical testing should be used for patients at risk for misrepresenting true tobacco use to ensure that tobacco users are identified and offered evidence-based treatment.[201,202] Treating tobacco use with evidence-based treatment within an encounter for the comorbid condition (integrated treatment) or by referring patients to dedicated cessation programs (parallel treatment) should consistently increase cessation rates. As recommended in the 2008 PHS Clinical Practice Guideline,[2] counseling and evidence-based pharmacology should be used in combination to increase cessation efficacy, though caution may be required with some medications in light of the comorbid diagnosis or treatment (eg, bupropion in patients taking tamoxifen for breast cancer).

While the research suggests that evidence-based interventions work for most smokers, it is important to note that novel methods may be required to specifically enhance cessation efficacy in subgroups who do not respond to traditional evidence-based treatments.[203] This review has illustrated the importance of understanding the mechanisms by which a comorbid condition can influence smoking cessation and/or treatment success. There is a clear need to identify tobacco treatment mechanisms as they are related to specific traits and symptoms associated with psychiatric and medical illnesses. This would make tailoring relevant for anyone with that particular trait or symptom, even if it did not cross a diagnostic threshold.

There is clearly much work needed to understand the associations between smoking and comorbid conditions. This includes understanding how smoking influences comorbid conditions as well as how comorbid conditions may influence smoking, from motivation to quit to response to motivation and cessation treatments. Future research considerations include:

1. Identifying the optimal time to address smoking cessation relative to receiving a new diagnosis, a change in prognosis or embarking on a new treatment regimen (ie, are patients more receptive immediately at the time of a new diagnosis or later, after absorbing the stress of the diagnosis?).
2. Identifying the optimal method and intensity to deliver cessation treatment in specific clinical environments, as well as the ideal professional to deliver the interventions (eg, clinicians vs. dedicated cessation counselors) and systems-level changes that could facilitate the provision of such treatment.
3. Calculating the cost benefits of smoking cessation treatments in different comorbid populations.

4. Identifying how smoking cessation treatment can be implemented in the context of multiple comorbid conditions, as is the case with many patients.
5. Evaluating the impact of psychiatric comorbidity in the context of treating tobacco use and other comorbid conditions.
6. Identifying how smoking and cessation affect comorbid disease outcomes.
7. Understanding the relations among smoking and other comorbidities not reviewed here (eg, diabetes, surgical complications).

These and many other more discrete questions require careful thought. However, they are increasingly relevant with the improvements noted in the management of comorbid conditions over the past several years.

In conclusion, traditional approaches to addressing tobacco use have focused on providing standard, evidence-based treatment to people who smoke in the general population. As we have argued in this article, there is a clear need to apply the same fundamental principles of providing evidence-based cessation treatment to patients with comorbid conditions within the context of treatment for their condition, given the preponderance of people who smoke who want to quit. Researchers and clinicians need to consider how the specific comorbid condition(s) could influence smoking cessation and how smoking cessation could influence the comorbid condition(s). This article represents a "call-to-action" by both tobacco treatment specialists and clinicians who treat comorbid conditions to develop a better understanding of how to integrate smoking and comorbid condition treatment and to promote the treatment of tobacco dependence for patients with these comorbid conditions to improve public health.

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