

# COVID-19 and Tobacco Use: A Review

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## ABSTRACT

Coronavirus disease-2019 (COVID-19) was acknowledged as a pandemic in March 2020. COVID-19 affected substance users by aggravation of stress and reduction of substance availability. This led to the proliferation of gray market, inadvertent consumption of toxic substances, withdrawal-related suicide attempts, and even completed suicide. Among these, a silver lining was an increased treatment-seeking behavior. Tobacco is a highly debated substance in the context of COVID-19, with contradictory and controversial evidence regarding the interrelationship between the two. Nicotine affects the expression of angiotensin-converting enzyme-2 (ACE-2), which acts as a cellular receptor for the entry of SARS-CoV-2. Cholinergic nicotinic stimulation to alveolar macrophages can also reduce cytokine release. This might be helpful during the cytokine storm phase of the illness. So nicotine may be a treatment option for COVID-19. Some counterintuitive data show a reduced prevalence of smoking among COVID-19 patients in comparison to the general population. Smoking and vaping-related lung injuries are proposed to be a contributory factor for increased mortality among adult males. Vaping may further increase vulnerability by acting as a fomite source for infection due to the sharing of the device. Lockdown has increased predilection for tobacco use and also restricted substance availability and treatment access. In this situation, various behavioral managements such as distraction techniques and relaxation exercises might be helpful to handle craving. Telemedicine and app-based interventions might also be helpful in some situations.

**Keywords:** COVID-19, Management, Substance use, Tobacco.

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## INTRODUCTION

Coronavirus disease-2019 (COVID-19) was acknowledged as a pandemic in late March 2020 and is rapidly spreading worldwide.<sup>1</sup> The COVID-19 pandemic has posed a unique challenge to humankind. The unknown nature of the illness created uncertainty, fear, and panic among people. Various preventive measures are being implemented at the national and international level to contain the spread of the infection. These include, but are not limited to social distancing, suspension of public gathering and nationwide lockdown. At the individual level, maintenance of hand hygiene, use of protective gears (like face masks), healthy diet, and refraining from substances are stressed upon. Tobacco smoking, being one of the commonest risk factors for respiratory illnesses, is in the list of caution.<sup>2</sup>

Currently, COVID-19 has spread in 215 countries worldwide, with around 9.8 million diagnosed cases and around 4.95 lakh deaths worldwide.<sup>3</sup> The first case in India was reported on 30th of January, 2020. In the next three and half months, the number of infected persons rose to a daunting number of around 5.3 lakhs, with a death toll of around 16,000.<sup>4</sup> Various models predict the peak of infection to occur between mid-July 2020 and October 2020, and the predicted total number of affected persons is around 120 million at the time of peak.<sup>5,6</sup>

Isolation, sustained lockdown, anxiety regarding job, loss of income, and infectivity of illness have gripped the psyche of commoners including substance users.<sup>7</sup> These negative emotions can presumably push a vulnerable individual to take refuge to substances, but there was severe crunch in the availability of substance due to lockdown. This is reflected by google search trends and newspaper reports. There was also some increase in search trend about methods of quitting substance use.<sup>8</sup> Simultaneously, there are reports of selling licit substances such as alcohol and tobacco in the gray market, poisoning with isopropyl alcohol in hand sanitizer in a desperate effort to substitute ethyl

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alcohol, and liquor theft at bars or liquor shops amid lockdown.<sup>9–11</sup> In this article, we will be reviewing the existing current literature regarding the co-occurrence of smoking and COVID-19.

## SEARCH STRATEGY

We wanted to review the literature about COVID-19, tobacco smoking, and their interrelation. For this, we have conducted a PubMed search with the following search items: (tobacco OR smoking OR nicotine) AND ("SARS-CoV-2" OR "COVID-19 infection"). This yielded 80 results. Most of the literature consisted of personal viewpoints and letter to the editor, and we have reviewed the existing data, after excluding the irrelevant articles.

## COVID-19 AND SMOKING

Coronavirus disease-2019 pandemic affected tobacco users as a double-edged sword. On one hand, the drive to use tobacco can increase due to stress, and on the other hand, the restrictions (lockdown, isolation, etc.) reduced the availability. A study consisting of 6,800 tobacco users across 5 countries (USA, Italy, UK, India, and South Africa) further elucidated this scenario. There were marginal increase in e-cigarette use, but at the same time, there was increase in the attempt to quit, which was due to the combined effect of fear of increased vulnerability and reduced

availability. Reduced availability also promoted stockpiling in some consumers, and restricted movement increased smoking at home, that may aggravate harm due to passive smoking.<sup>12</sup>

The role of tobacco use as well as that of nicotine—the main ingredient of tobacco in pathogenesis and management of COVID-19—is highly debated. We will be discussing these aspects along with the current understanding of the same as follows.

### Potential Treatment Target—ACE-2 and Nicotinic Cholinergic Receptor: Is Nicotine a Suitable Arrow?

Till now, there is no proven treatment for this illness, and at present, there is a desperate search for treatment options. Along with viricidal agents and vaccines, a wide array of approaches such as immunomodulator (monoclonal antibody, steroid, etc.), passive immunotherapy (convalescent plasma), decoy molecule (ACE-2) are being explored to enhance our armamentarium against this novel threat.<sup>13,14</sup>

#### *COVID-19 Pathogenesis in Terms of ACE-2 and Nicotinic Receptor*

SARS-CoV-2 is a single-stranded RNA virus that uses ACE-2 as a receptor for cellular entry. The alveolar epithelial cells and macrophages are abundant in ACE-2 receptors. Lung is the commonest and most severely affected organ, and acute respiratory distress syndrome (ARDS) is one of the severe and potentially fatal complications of COVID-19 infection. It occurs due to the rapid release of cytokines from alveolar macrophages. Vagal nerve inhibition may inhibit the cytokine release by its action on nicotinic acetylcholine receptor (nAChR)  $\alpha 7$  subunit on macrophages.<sup>15</sup>

Now there is a dilemma: on one hand, tobacco smoking is considered to be a risk factor for the complicated COVID-19 infection, whereas the active ingredient nicotine is a potential therapeutic target for the same. So where do we stand?

#### *Evidence of Nicotine in COVID-19 Management*

The above observation simultaneously opens up the possibility of use of nicotine in COVID-19 treatment. Nicotine was found to downregulate ACE-2, and as a result, nicotine was thought to inhibit ACE-2-mediated virus entry in the susceptible cells. This postulation is questioned when recent studies pointed toward upregulation of ACE-2 in smokers. This actually points toward increased susceptibility to COVID-19 among persons using tobacco but still suggests that ACE-2 might become a possible therapeutic target.<sup>16</sup> Another postulation suggests that SARS-CoV-2 like many other neurotrophic viruses competes with nicotine in binding with ACE-2, and as a result, in spite of ACE-2 upregulation, nicotine actually reduces virus entry at the cellular level.<sup>17</sup>

An alternative proposed mechanism of action of smoked tobacco in protecting from COVID-19 is squamous cell metaplasia, which is almost always present among smokers. It is proposed that due to metaplastic epithelial changes, the SARS-CoV-2 cannot penetrate the epithelial cell membrane in the smokers, which exerts the protective effect.<sup>18</sup>

Nicotine acts upon the nicotinic acetylcholine receptor (nAChR)  $\alpha 7$  subunit on macrophages to exert its anti-inflammatory effect. As a result, nicotine or its congeners might be a potential therapeutic modality especially in the cytokine storm of COVID-19 infection.<sup>19</sup>

#### *Does Smoking Reduce COVID-19 Infection?*

The prevalence of smoking among hospitalized COVID-19 patients was first assessed in China. Increased prevalence of tobacco smoking was expected among these patients, but the result was

counterintuitive. In a systematic review of 13 studies (11 were from China), the prevalence of current smoking among hospitalized patients with COVID-19 ranged from 1.4% to 12.6% across 13 studies, which is significantly lower than the usual prevalence of smoking in the Chinese population. This difference retained its significance even when the former smokers were also included as current smokers in the analysis.<sup>20</sup> Similarly, lower than general population prevalence of tobacco use was found among hospitalized and nonhospitalized COVID-19 patients in USA.<sup>21</sup>

These data are not beyond question, and there is always a possibility of under-reporting of actual prevalence of smoking. On the other hand, the presence of multiple toxic compounds in the cigarette smoke undoubtedly increases the risk of pulmonary damage and makes the possibility of recommendation of tobacco smoking for COVID-19 indefensible.<sup>22</sup> The data on smokeless tobacco use are not available. Smokeless tobacco is put to mouth by hand, and there is frequent sharing of substance, and the users frequently spit the saliva-laden substance after attaining the kick. These habits may pose a threat of increased spread of COVID-19.<sup>8</sup>

### Can Smoking Act the Other Way around?

In spite of some evidence about the protective role of nicotine, we cannot turn a blind eye upon the mounting evidence in the contrary. Various studies show a significantly higher mortality among adult males with respect to females and pediatric COVID-19 patients, and one of the proposed factors for this difference was higher rates of smoking among males.<sup>23–25</sup> A relatively early meta-analysis, assessing relationship between adverse outcome and smoking in patients with COVID-19, showed that smokers were around 1.4 times more likely to have severe symptoms of COVID-19 and are around 2.4 times more likely to require ICU admission or mechanical ventilation or die with respect to nonsmokers.<sup>26</sup> A recent meta-analysis of 19 studies across the globe assessed the progression of COVID-19 and smoking behavior of the patient. Smoking was found to be significantly associated with the progression to a severe disease (OR 1.91, 95% confidence interval [CI] 1.42–2.59,  $p = 0.001$ ), which may lead to the need for ICU admission, mechanical ventilation, or to death.<sup>27</sup> The proposed mechanisms for the adverse outcomes are more serious systemic conditions, including cardiovascular and respiratory comorbidities along with immunological disturbances among regular smokers.<sup>28</sup>

There are some concerns regarding the role of vaping in COVID-19. There is a dearth of literature regarding the outcome of COVID-19 in relation to vaping. The current knowledge about the detrimental effect of vaping on respiratory and cardiovascular system makes it a potential aggravating factor for COVID-19. There are some claims about the protective roles of vaping by increasing humidity or acting as vehicle for the delivery of some drugs (like oregano oil, etc.) in the lung. None of these claims is substantiated by scientific evidence. Besides these, as a result of frequent sharing, vaping device may actually act as a source of virus contamination.<sup>29</sup>

### COVID-19-related Lockdown and Use of Tobacco

In India, the prevalence of tobacco smoking was around 11% and of smokeless tobacco use was around 21.4% in 2016–2017.<sup>30</sup> In spite of a gradual decreasing trend, this number is quite alarming considering the population in India, and the potential synergistic effect of COVID-19 and smoking may be more worrisome. The nationwide protracted lockdown increased worry, tension, and frustration among people (due to the pandemic itself, limitation of movement, isolation, unemployment, etc.), which is a known cause

for a surge in addictive behavior including smoking.<sup>8</sup> The problem is further complicated by the sudden announcement of lockdown leading to severe supply crunch, and this opened the road to gray market, where cigarettes were being sold at much higher rate than the printed price.<sup>31</sup> Those who want to access treatment for tobacco use disorder find themselves in a deeper problem, as many of the nonemergency health facilities including addiction services were closed to contain the spread of infection.<sup>32</sup>

### Treatment of Nicotine Dependence amid Lockdown

In spite of the mounting stress, lockdown may be viewed as an opportunity to get rid of problematic substance use, especially nicotine. The stringent supply reduction compelled almost everyone to cut down the amount of smoking.

Several agencies, including WHO, came up with materials advocating various behavioral management techniques for the control of tobacco craving. Besides the behavioral management, WHO also advocates the use of nicotine replacement therapy wherever applicable.<sup>33</sup> The behavioral management strategies can also be used for smokeless tobacco users.<sup>34</sup>

Currently, telemedicine is a proposed alternative for face-to-face consultation, and various deaddiction services, including ours are trying to explore the potential of telemedicine. Counselling and nicotine replacement therapy (NRT) may be accessible through teleconsultation. Bupropion, the other widely prescribed medication, can only be continued through follow-up teleconsultation, as per current guidelines, but the guidelines are changing depending upon the changing scenario.<sup>35</sup>

Although the final aim is to be completely tobacco-free, but that seems to be a distant dream, given the intricate web of monetary investment, lobbying, and job. As a result, the fight against tobacco is fought in a different front, where the individual is to be assisted to stop using tobacco successfully and permanently.<sup>36</sup>

### CONCLUSION

The current knowledge about the relationship between tobacco use and COVID-19 is in an evolving phase. As a result, there is a lot of contradictory data and information available, and the interpretation of the data often varies widely when seen from different point of view. Currently, the research projects are mostly small-scale ones and, in many a cases, are limited within personal viewpoints or hypothesis. More robust researches may actually come to a more defensible conclusion. As a matter of fact, smoking, smokeless, and vaping have deleterious effects on respiratory system, and this must not be undermined while assessing the so-called potential therapeutic role of nicotine in COVID-19 infection. Regarding the treatment of nicotine dependence including substance use disorders during the trying time of pandemic, there is a lot of unmet needs. Addiction services are still struggling with the newly evolving challenges.

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