



Letter

Beyond Smoking Cessation: Investigating Medicinal Nicotine to Prevent and Treat COVID-19

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In the absence of treatment or a vaccine, the SARS-CoV-2 pandemic challenges the medical community to identify novel containment strategies. Changeux et al.¹ have proposed the nicotinic hypothesis—that nicotinic acetylcholine receptors may be a therapeutic target to reduce SARS-CoV-2 infection and mitigate COVID-19 disease. Testing the nicotinic hypothesis has implications to prevent and treat COVID-19 disease among billions of patients and health care providers, including those who smoke cigarettes and those who do not.

Mounting epidemiologic evidence of lower SARS-CoV-2 infection rates among smokers² may in fact be explained by exposure to nicotine, as opposed to the thousands of harmful chemicals contained in cigarette smoke. Nicotine modulates the renin–angiotensin–aldosterone system, the physiologic cascade implicated in pulmonary, cardiovascular, renal, and neurologic complications of COVID-19 pathogenesis.³ Nicotine and cigarette smoke have been reported to decrease levels of angiotensin-converting enzyme 2, the putative receptor for SARS-CoV-2, in multiple organs.⁴ In the lungs, increased angiotensin-converting enzyme 2 expression has been documented in individuals who smoke and those with chronic obstructive pulmonary disease who are undergoing bronchoscopy.⁵ The clinical significance of these findings for SARS-CoV-2 infection risk is unclear. If indeed nicotine lowers angiotensin-converting enzyme 2 expression, thereby denying viral particles entry into cells, then exogenous nicotine administration may reduce SARS-CoV-2 infection rates. Nicotine may also modulate COVID-19 disease severity through the cholinergic anti-inflammatory pathway, inhibiting macrophage-driven hyperinflammation and platelet reactivity. Medicinal nicotine has been safely used for tobacco treatment in millions of patients for decades, including the acutely ill, and is currently under investigation in randomized controlled trials in nonsmokers to treat neurological conditions.⁶

Before medicinal nicotine could be recommended for COVID-19, evidence is needed. French researchers recently announced plans for a randomized controlled trial to test medicinal nicotine to

prevent and treat COVID-19 in providers and patients with moderate and severe illness.¹ Similar US studies would likely be needed to obtain Food and Drug Administration approval for this indication. A complementary approach could leverage data from existing National Institutes of Health-sponsored randomized controlled trials in nonsmokers, such as an ongoing trial testing whether medicinal nicotine improves symptoms in older adults with mild cognitive impairment.⁶ Data from this trial could be analyzed to examine whether medicinal nicotine alters the risk of acquiring SARS-CoV-2. Further analyses could investigate a potential moderating role of genetic variation in hepatic nicotine metabolism or nicotinic acetylcholine receptors. Finally, observational cohorts may be leveraged to address the nicotinic hypothesis provided they are sufficiently large and contain enough clinical information to account for confounding, as well as to distinguish between exposure to medicinal nicotine and exposure to other tobacco products.

Distinguishing medicinal nicotine treatment from cigarette smoking for the prevention and treatment of COVID-19 is critical: simply stated, smoking has no therapeutic role. In contrast, medicinal nicotine is an Food and Drug Administration approved, inexpensive, over the counter, readily available therapy with a longstanding safety record including low addiction potential, and few contraindications. Given the observed lower rates of SARS-CoV-2 infection among individuals who smoke, the biological plausibility of medicinal nicotine to lower infection and mitigate disease severity, and the feasibility of using medicinal nicotine for individuals who do not smoke, medicinal nicotine should be rapidly examined for a role in the prevention and treatment of COVID-19.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at <https://academic.oup.com/ntr>.

Declaration of Interests

None declared.

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