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Abstract- People with opioid use disorder (OUD) have rates of cigarette smoking approaching 90% and smoking cessation programs are rarely effective. The relationship between long-term opioid exposure and smoking has been epidemiologically observed but not well understood. Nicotine interacts with the nicotinic acetylcholine receptors in the central and peripheral nervous systems, which are involved in anxiety, cognition, sleep, arousal, and pain perception. Cigarette smoking triggers the release of dopamine in the brain. There is equivocal evidence that nicotine may have an analgesic effect, but paradoxically, smokers tend to have higher pain intensity levels than nonsmokers. Pharmacologic treatments for nicotine dependence were often studied in trials that routinely excluded subjects with opioid dependence. Further, the association between smoking and long-term opioid use sometimes includes mental health disorders and/or chronic pain. In fact, smoking may also be comorbid with chronic pain. It has been speculated that smoking, particularly at a young age, may be predictive of OUD. While smoking is also associated with other forms of substance abuse, the association between OUD and tobacco is particularly intriguing and likely involves common neurobiological pathways.

I. INTRODUCTION

People in the United States with opioid use disorder (OUD) have a rate of cigarette smoking of 84% to 94%, many times greater than 14% rate of smoking in the general population.¹ These high rates of smoking occur in those taking illicit opioids, those taking prescription opioids as indicated and under medical supervision, recreational and nonmedical opioid users, and those on opioid maintenance therapy (OMT) with buprenorphine or methadone.²⁻⁵ Among adults seeking treatment for a substance use disorder, smoking prevalence is greater among those with OUD than for

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alcohol or other substance use disorder.¹ While many in these populations express an interest in quitting smoking, the success rate for cessation therapy, even with pharmacologic treatment and clinical supervision, remains low.^{6,7}

By the same token, OUD occurs more frequently in daily smokers (2.6%) or nondaily but regular smokers (1.5%) than among non-smokers (0.5%) or never-smokers (0.2%). It has been suggested, and challenged, that cigarette smoking might even be a “gateway drug” to opioid use.^{8,9} An algorithm of three statistical predictors for adult OUD were developed in the United States: smoking status, mental health disorder, and nonopioid substance use disorder.¹⁰

The connection between smoking and OUD has long been clinically observed, but studies have been primarily epidemiologic rather than mechanistic or medical. The primary objective of this narrative review was to survey the literature for an understanding of why there is such a strong association between OUD and smoking and how this might help guide future efforts at opioid rehabilitation and smoking cessation.

II. METHODS

This is a narrative review on the subject of OUD and smoking aimed at better understanding their mutual association. In October 2021, the PubMed database was searched for the terms “smoking AND opioid use disorder OR OUD” with no delimiters as to type of article or date. A total of 1,078 results were retrieved, of which 100 were randomized clinical trials. Google Scholar was also searched as were the bibliographies of many articles retrieved. The authors excluded articles that were not in English or did not explore the specific association between smoking and OUD. A total of 60 articles were used.

III. RESULTS

Nicotine, the main alkaloid of the tobacco plant, is a botanical insecticide produced in tobacco leaves and making up about 1.5% of the weight of commercial tobacco.¹¹ About 99% of nicotine in tobacco occurs as the levorotary X-isomer rather than the R-isomer.¹¹ When tobacco is burned, nicotine is distilled and may be

transported on particulate matter ("tar") which, when inhaled, enters the lungs. Commercial American cigarettes have a pH of around 5.5 to 6.0, which allows ionization of the nicotine so that there is little buccal absorption.¹² More alkaline types of tobacco, such as pipe tobacco (pH \geq 6.5), can be better absorbed in the mouth.¹² When cigarette smoke reaches the tiny airways and alveoli of the lungs, nicotine is rapidly and directly absorbed into the bloodstream and the alkaline content of liquid in the lungs (~ pH 7.4) allows for rapid membrane transmission. In fact, nicotine can reach the brain in about 10 seconds by smoking a cigarette, which is more rapid than by intravenous administration.¹³ Cigarette smoking is self-titrating in real time, because smokers can adjust their nicotine intake with depth of inhalation, amount inhaled per puff, and the rate at which they smoke.¹⁴

Nicotine has an affinity for brain tissue and smokers have enhanced cerebral receptor capacity compared to nonsmokers, which reverses with smoking cessation.¹⁵ While there are numerous nicotine metabolites, about 80% of all nicotine in humans is converted to the cotinine metabolite in a two-step process. First, nicotine is metabolized via the cytochrome-P (CYP) 2A6 enzyme into the nicotine- $\Delta^{1(5)}$ -iminium ion which exists in equilibrium with the 5'-hydroxynicotine. In the next step, this metabolite is catalyzed by the cytoplasmic aldehyde oxidase.¹⁶ Only about 4% to 7% of nicotine metabolites are the nicotine N'-oxide metabolite.¹⁶ About 10% to 15% of cotinine is excreted unchanged in urine.¹⁷ Total clearance of nicotine takes on average 1200 ml/min and is slower in smokers than nonsmokers.^{16,18} Nicotine metabolism is often described as the ratio of 3'-hydroxycotinine to cotinine (3HC) which can be readily tested in blood or saliva.¹⁹ The ratio of 3HC to cotinine has been termed the nicotine metabolite ratio (NMR) and as used as a marker for nicotine activity.²⁰

As an alkaloid, nicotine interacts with ion channels in the nicotinic acetylcholine receptors (nAChRs), which are distributed in both central and peripheral nervous systems and handle a range of functions including sleep, anxiety, cognition, arousal, and pain perception.²¹ There are two types of nAChR with different structures: neuronal and muscle-type. All nicotinic receptors possess five subunits symmetrically arranged around a central pore. These subunits each possess four transmembrane domains with the N- and C-termini outside of the cell. These receptors act as non-selective ligand-gated ion channels, where the central pore can be opened by agonists, such as endogenous acetylcholine or exogenous nicotine.²¹

Nicotine may have analgesic properties at the nAChRs,²² as demonstrated in preclinical²³ and clinical studies.²⁴ Paradoxically, smokers tend to have higher pain intensity levels than nonsmokers and are at increased risk for developing certain painful syndromes,

such as low back pain.^{25,26} Functional imaging studies suggest that depression and smoking utilize common neurobiological pathways and are both associated with the release of dopamine in the brain.²⁷

Nicotine dependence has been found to be more prevalent among people with mental health disorders and/or substance use disorders.²⁸ In the United States, people with mental health disorders and/or substance use disorders make up 22% of the total population but consumer 44% of all cigarettes.²⁸ Nicotine is a sympathomimetic drug that releases catecholamines, accelerates heart rate, enhances cardiac contractility, possesses vasoconstrictive properties, and has been associated with transient increases in blood pressure.²⁹ Prolonged exposure to a combination of nicotine plus opioids can result in binding to the nicotinic receptors of the neurons that contain opioid peptides, resulting in a release of endogenous opioids.^{30,31} Chronic nicotine exposure can disrupt the body's endogenous opioid system, which could result in reduced pain thresholds and cross-tolerance to opioid analgesics.²² A study based on data from the National Survey on Drug Use and Health (n=58,971) found that smokers who were dependent on opioids were more dependent on nicotine than nonsmokers without opioid dependence.³² This would explain why smokers need higher doses of opioids compared to nonsmokers to obtain equivalent analgesic benefit.^{33,34} Furthermore, chronic nicotine exposure may sensitize dopaminergic systems to opioids.³⁵ The brain's reward and reinforcement systems involved in the perpetuation of opioid dependence may be enhanced by nicotine.³⁵

In general, people who take opioids for medical or nonmedical reasons are more likely to smoke and smoke more cigarettes per day than those who do not take opioids.²⁰ Nicotine metabolism varies among individuals and NMR values have been associated with specific smoking behaviors.³⁶ For example, rapid metabolizers of nicotine, as measured with the NMR, tend to smoke more cigarettes per day than slow metabolizers. Women are generally faster nicotine metabolizers than men and this metabolic differential increases during pregnancy.^{16,37}

It is not entirely clear why smoking and OUD are so closely associated. It has been suggested that the stimulating effects of nicotine might help fight the sensation of drowsiness and somnolence induced by opioids.³⁸ In people with OUD and chronic pain, it has been speculated that smoking may distract from painful symptoms, alleviate malaise, and serve as a coping mechanism.^{39,40} However, nicotine dependence has been associated with more severe chronic pain symptoms,⁴¹ although smoking was not associated with exacerbated pain intensity immediately following certain types of surgery.⁴² This analgesic benefit may be short lived. A retrospective chart review of 178 total hip or

knee arthroplasty patients found that those who smoked required an average of 90% more morphine milligram equivalents (MMEs) in the first three months after surgery than nonsmokers.⁴³ OUD is comorbid with a number of mental health conditions, including depression, and both are linked to higher rates of smoking but this relationship is not well studied.³⁴

It can be challenging for any patient population to quit smoking, but successful smoking cessation is rare among individuals with OUD. There are knowledge gaps in pharmacologic treatments for smoking cessation among people with OUD, as clinical trials of these treatments often excluded those with OUD or those taking buprenorphine or methadone for opioid maintenance therapy (OMT).⁴⁴ Despite the fact that the vast majority of individuals with OUD are current smokers and that it is well known that smoking increases morbidity and mortality, most opioid treatment centers do not offer smoking cessation programs.⁴⁵ It has been argued that people with OUD and their treatment providers foster a pro-smoking culture and most people with OUD have small social circles where smoking is considered normal and accepted.⁴⁶ Indeed, for people struggling to with opioid addiction, a chaotic lifestyle, and other difficult issues, smoking may seem to be a relatively a minor problem. Many people trying to navigate issues of addiction, legal problems, ill health, financial instability, broken relationships, disrupted careers, and numerous other difficulties may find smoking an acceptable stress reliever.

It is likely that certain neuroadaptive interactions between opioids and nicotine make it more difficult for a person exposed long-term to opioids to stop smoking.⁴⁷ Individuals with any type of substance use disorder have only about 25% the success rate with smoking cessation than others.³² It has been suggested that OUD may exacerbate the symptoms of nicotine withdrawal, but evidence is not strong.⁴⁸ In adults undergoing rehabilitation for OUD (n=22,046) or alcohol use disorder (n=15,251) at 30 days, cigarette smoking had decreased slightly in the alcohol use disorder population but remained the constant for those with OUD.⁴⁹

In a 24-week study of OUD patients taking buprenorphine or extended-release naltrexone for maintenance, naltrexone patients smoked fewer cigarettes per day on average (11.4) than buprenorphine patients (13.3).² In a study of patients taking naltrexone for illicit OUD, smoking was reduced by 29% from 14.4 to 9.8 cigarettes per day at one month and decreased further to 8.6 per day at two months.⁵⁰ The role of naltrexone as an effective aid in smoking cessation for people with OUD suggests that there may be a pharmacologic interaction between opioids and nicotine. However, a meta-analysis of eight studies (n>1200) could not find strong evidence in support of the use of naltrexone either alone or as an adjuvant agent in a smoking cessation program, but these

studies were for general patient populations rather than those with OUD.⁵¹

People with OUD may exhibit different patterns of nicotine dependence than those without OUD.⁵² At baseline, smokers with OUD had more severe nicotine withdrawal symptoms than smokers without OUD, but after a two-week smoking cessation program, withdrawal patterns were similar for those with or without OUD. Smokers without OUD experienced a flare in withdrawal symptom intensity right after embarking on a quit-smoking program, a pattern not observed among smokers with OUD, who may have mitigated their early withdrawal symptoms with opioid replacement therapy. Cravings for cigarettes occurred in both groups but those with OUD had diminished cravings at the start of the program, while those without OUD had maximal cravings at the outset.⁵²

The age at which smoking started may be correlated to OUD. Those who began to smoke before the age of 14, compared to those who started smoking as adults ≥ 18 years, were more than twice as likely to report nonmedical opioid use in the past year.⁵³ The Youth Risk Behavior Survey conducted in the United States in 2018 (n=10,175), surveyed American adolescents between 12 and 17 years and found 13.8% reported having used opioids recreationally.⁵⁴ Adolescents who smoked were more likely to have used opioids; among those young people who reported smoking cigarettes, the adjusted odds ratio for recreational opioid use was 2.49.⁵⁴ Even parental smoking increased an adolescent's risk for nonmedical opioid use. In a database study of 35,000 parent-child dyads, in children between the age of 12 and 17, nonmedical use of opioids was more likely to occur in children with parents who smoked, regardless of whether the child smoked.⁵⁵

Many people with OUD express an interest in quitting smoking. A cross-sectional study of 68 patients receiving outpatient buprenorphine maintenance for OUD found that 88% were current smokers, 8% former smokers, and 4% had never smoked. Of those who smoked, 83% had tried to quit at least once.⁵⁶ Besides putative opioid-nicotine interactions, there are other barriers to smoking cessation for people with OUD including a lack of access to treatment, limited understanding of smoking cessation tools, prioritization of other more pressing medical and social issues, and lack of insurance.⁴⁵ Many smoking cessation treatments rely on nicotine delivered via transdermal patches, sprays, gums, lozenges, or inhalers. However, the experience of nicotine consumption using these methods is vastly different from smoking. The nicotine patch, for example, enters the system gradually, is relatively slow to reach the brain, and cannot be regulated by the user as a smoker might do with deeper puffs.¹⁶ Thus, the use of nicotine replacement therapy may not be as satisfying as smoking.

Opioids are indicated for acute and chronic painful conditions and are sometimes street opioids are taken to self-medicate undiagnosed pain. Chronic pain appears to be associated with cigarette smoking and it is unclear how opioid use factors into this association. In a cross-sectional study from a single European multidisciplinary pain center (n=98), the rate of smoking was double that in the general population and 54% of these pain patients took opioids. Smokers in this population used opioids more frequently and at higher doses than former smokers and nonsmokers.⁵⁸ A cross-sectional naturalistic study of 798 adults with chronic noncancer pain taking opioid analgesics medically for ≥ 6 months found that 216 developed OUD and the odds ratio adjusted for other risk factors was 14.0 for current smokers to develop OUD.⁵⁷ Smoking was not the sole risk factor for a smoker to develop OUD: others were younger age, unmarried status, lower socioeconomic status, less education, and the severity of the pain. In that study, 81% of chronic noncancer pain patients who had OUD were smokers compared to 23% of those who had chronic noncancer pain but did not develop OUD.⁵⁷ Smoking rates are higher for those who use either illicit or prescribed opioids. Of patients who receive medically supervised long-term opioid treatment to manage pain, smokers outnumber nonsmokers.⁵⁹

Complicating this picture is the association of chronic pain with depressive symptoms.³⁴ Chronic pain patients who smoke have significantly higher rates of depression and take more MMEs daily than chronic pain patients who do not smoke.³⁴ In fact, it has been suggested that smoking may be a predictor of depression in chronic pain patients.³⁴ Likewise, smoking and chronic pain may be comorbid,^{39,60} in that smoking is associated with a greater risk for developing chronic pain and the number of cigarettes smoked per day correlates to the increased risk for chronic pain. Smokers with chronic pain report more numerous pain sites, pain of greater intensity, higher degrees of dysfunction, and more long-term disability than nonsmokers.²² Nicotine dependence is itself associated with more severe symptoms of chronic pain.⁴¹ Smoking in a chronic pain patient has been proposed as a risk factor for substance use disorder, including OUD.⁶¹ Smoking, prolonged opioid exposure, chronic pain, and depressive symptoms frequently occur concurrently but their exact interplay is not elucidated.

IV. DISCUSSION

Opioids are associated with powerful neuroadaptive changes in the brain that can help alleviate pain, stimulate reward circuits, produce euphoria or feelings of well-being, and help soothe anxiety. For those with long-term physiologic dependence, taking opioids can restore feelings of "normalcy" and stave off withdrawal symptoms. Thus, it

is perhaps unrealistic to think of opioids as simply pain relievers, because their psychoactive effects may help mitigate symptoms of mental illness, improve coping skills, and provide pleasure while their physiologic effects still cravings, restore a sense of well-being, prevent distressing symptoms, and stimulate the brain's reward circuits. Cigarette smoking exerts powerful effects on the nicotinic receptors, may release dopamine, and enhance the effects of opioids on the brain. The symbiosis between nicotine and opioid dependence has been epidemiologically observed but trivialized as people with OUD or those on long-term opioid therapy have other medical issues which take precedence. Nevertheless, it must be recognized that nearly all people with OUD as well as the majority who take prescription opioids under medical supervision are smokers and have great difficulty giving up cigarettes. Smokers lose 10 years of life compared to those who have never smoked and smoking is associated with numerous comorbid conditions.⁶²

An important special population of those with OUD and nicotine dependence are pregnant women. While about 20% of smokers quit as soon as they learn they are pregnant, the majority of smokers smoke over the course of their pregnancy,⁶³ even though it is well known that smoking is associated with poor pregnancy outcomes.⁶⁴ Nicotine metabolism accelerates during pregnancy, making cessation even more difficult.³⁷ For this special population, alternative interventions to stop smoking are urgently needed.

Actually, the OUD and chronic opioid therapy population has been generally overlooked in the search for smoking cessation strategies. Many clinical trials of pharmacologic treatments excluded those with OUD. While there may be psychological and social reasons that people with OUD continue to smoke or regard smoking as a low-risk acceptable activity, the association between OUD and smoking likely is based on physiologic factors. It is plausible that smoking enhances some of the pleasurable psychoactive or beneficial analgesic effects of opioids. Discontinuing opioid therapy or rehabilitation from OUD is challenging and relapse is common; smoking is another burden on this population. Better pharmacologic treatments and more effective psychosocial interventions are needed to help patients navigate through these dual dependencies.

Our review of OUD and smoking revealed that it was not only OUD and smoking that were so closely related but also depression and chronic pain. The exact interplay of these conditions remains to be elucidated. Like people with OUD, people with mental health disorders have been historically excluded from clinical trials for pharmacologic smoking cessation treatments.⁶⁵ Studies of antidepressants such as bupropion have shown promise for smoking cessation, but this agent is also associated with psychiatric adverse events.⁶⁶ There

is also evidence in support of varenicline and nortriptyline to aid in smoking cessation but these agents have not been studied in the population regularly exposed to opioids.⁶⁷

Smoking has also been associated with the use of other substances, such as cocaine or alcohol use disorder. The mechanisms behind these associations are likely to be fundamentally different than the connection between opioids and nicotine. While cocaine users are two to four times more likely to smoke cigarettes than the general population, the enhancement of cocaine's psychoactive effects by nicotine are modest.^{68,69} While nicotine appears to only slightly potentiate the pleasurable effects of cocaine, both nicotine and cocaine can result in hypertension and tachycardia, making cigarette smoking particularly dangerous for those using cocaine.⁶⁸ It has been suggested that the powerful stimulating effects of cocaine can encourage people to smoke or smokers to smoke more.⁷⁰ The association between cigarette smoking and polysubstance drug use disorder remains unknown.

V. CONCLUSION

While long observed in clinical practice, the underpinnings of the association between prolonged opioid exposure and cigarette smoking have not been elucidated. Nicotine may enhance the reward effect of opioid use and may possess some analgesic properties as well. People taking opioids long term can find it difficult to stop smoking and conventional pharmacologic treatments do not appear to be effective in this population. Further, the link between smoking and opioid use may encompass chronic pain and depression in ways that are not yet clear. Since smoking is associated with significant morbidity and mortality, further study is needed, particularly to assist smokers taking opioids who want to quit. This is an urgent unmet medical need for pregnant OUD patients, most of whom are not able to quit smoking during their pregnancy.

Disclosures

The authors have no relevant disclosures.

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