

# Beyond Vaping: Psilocybin for the Treatment of Tobacco Use Disorder.

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Ceman's [1] review, in this issue, examines the potential uses of psilocybin with associated psychotherapy for the treatment of numerous conditions. One such condition is tobacco use disorder and, more specifically, cigarette smoking. The Centers for Disease Control and Prevention (CDC) estimated in 2017 that "14.0% (34.3 million) of U.S. adults were current cigarette smokers. Of these, 75.0% smoked every day [2]". The CDC also notes that cigarette smoking is more common in individuals of lower socioeconomic status, with more comorbid medical and psychiatric conditions. They state that "1 in 4 (or 25%) of adults in the U.S. have some form of mental illness or substance use disorder, and these adults consume almost 40% of all cigarettes smoked by adults overall [3,4]". Cigarette smoking is responsible for the death of "more than 480,000 each year. In addition, smoking-related illness in the United States costs more than \$300 billion a year, including nearly \$170 billion in direct medical care for adults and \$156 billion in lost productivity [5,6]". Any treatment modality that can reduce or mitigate the costs associated with cigarette smoking morbidity and mortality should strongly be considered, if not wholeheartedly embraced.

Initially, this novel treatment modality was thought to have arrived in the form of electronic cigarettes (e-cigarettes), which allow users to inhale nicotine separate from tobacco in a process similar to smoking which is commonly referred to as "vaping." There is a high level of heterogeneity among e-cigarettes, but in general, they are defined as "battery-powered devices which simulate tobacco smoking by producing a heated

vapor that resembles smoke." The liquid solution is heated by an electric heating element, typically referred to as an atomizer or cartomizer, until the liquid transitions to a vapor [7]. The first known e-cigarette was patented in 2003 and first made available for sale in 2007 [7]. As of 2014, there were over 450 different brands and over 7,700 different flavors available for purchase [7]. Propylene glycol and vegetable glycerin are often added to the nicotine and flavoring to increase flavor and vapor production, respectively [7]. Figure 1 [7] details the design, associated parts, and functions of an e-cigarette:



The Federal Drug Administration (FDA) was given authority over tobacco products starting in 2009, but at that time the FDA deemed e-cigarettes to be a "drug delivery device" which meant that all e-cigarettes were subject to the regulations established under the Food, Drug, and Cosmetic Act of 1938 [8]. This designation meant that e-cigarette producers had to meet additional standards to bring their product to the market compared to if e-cigarettes had been classified as a "tobacco product." Manufacturers of e-cigarettes sued the FDA and won, meaning that e-cigarettes were classified as a tobacco product, and the FDA released a revised ruling in 2016 [9]. While

this ruling allowed e-cigarettes to be sold like cigarettes, it had the unintended consequence of preventing e-cigarettes from being marketed as a smoking cessation device. According to FDA regulations, e-cigarettes were essentially no different from a cigarette insofar as they were a nicotine delivery system [10]. This decision created a perverse incentive and resulted in some e-cigarette companies creating a marketing campaign that, at the very least, appeared, if this wasn't the explicit intent, to target teens and young adults [11]. Likely in part as a result of these campaigns, the largest demographic of individuals who report vaping is 18-24-year-olds, [12] and the rate of high school seniors who "reported smoking in the 30 days prior" was 20.9% in 2018 almost double the rate from 2017 [13]. These factors led to a growing concern among parents and regulators about vaping in this population, and this was before the epidemic of vaping associated lung injuries (VALI) that began to occur in 2019.

VALI has become an extremely contentious topic within the media, who have done an abysmal job of reporting the facts surrounding these injuries. According to the latest information from the CDC as of November 2019, there have been "2,172 EVALI cases to the CDC, including 42 (1.9%) EVALI-associated deaths" with 77% of these patients being under the age of 35 [14]. Additionally, 83% of hospitalized patients and 84% of individuals not hospitalized for VALI reported the use of THC-containing products [14] with examination of lung tissue from 29 patients from 10 states showing that all tissue samples contained vitamin E acetate oil. The finding of vitamin E acetate oil is extremely significant since the initial coverage of VALI strongly implicated nicotine-containing e-cigarettes and led to discussions about additional regulation and even a total ban of e-cigarettes. A ban would be a completely unjustified overreaction if it were to occur. E-cigarettes have only been on

the market for just over a decade before the start of this epidemic, which seems to be overwhelmingly linked to the inappropriate use of mostly unregulated THC-containing compounds, there has been little to no evidence that nicotine only solutions can cause VALI. These results are true not only in the United States but also in the United Kingdom and other countries that have been selling e-cigarettes for roughly the same period.

The benefits of properly used e-cigarettes far outweigh the risks of use, especially when compared to traditional cigarettes. Cigarettes contain over 7000 different compounds, over 60 of which are known to be carcinogenic [15]. By contrast, the additives in e-cigarettes, such as propylene glycol, vegetable glycerin, and associated flavorings, are generally well-tolerated and used in the production of numerous edible compounds. Cigarettes and e-cigarettes both pose a fire hazard, whether through combustion with cigarettes or mechanical failures with the vaporizer or heating element in e-cigarettes. Additionally, both can result in burns to the skin and irritation of the mucosa when inhaling. Tobacco products and e-cigarettes both contain nicotine which is a highly addictive substance that has been partially implicated as a causative agent in an extensive number of medical conditions but is also touted by proponents as aiding with attention and improving cognition. Evidence supporting the majority of these claims, both for and against, remains extremely limited, and most studies have not adequately demonstrated an association between pure nicotine use and either positive or negative outcomes [16]. Despite all of these potential risks, the evidence that e-cigarettes are safer than traditional cigarette use is clear and indisputable. In 2015 Public Health England concluded that e-cigarettes were 95% less harmful than smoking [17]. Further research

has shown that e-cigarettes reduce exposure to particulate matter, carbon monoxide, and other toxic and potentially harmful constituents [18].

While e-cigarettes are a viable and preferable alternative to traditional tobacco use, their effectiveness in the treatment of tobacco use disorders has only limited evidence. This lack of evidence is due in large part to the fact that e-cigarettes cannot be marketed as smoking cessation devices given the FDA's previously mentioned designation as a tobacco product, thus limiting potential research investigations. However, a 2018 randomized control trial (RCT) looking at smoking cessation rates compared an e-cigarette group to a nicotine replacement therapy (NRT) group and found that at one year the e-cigarette group had an abstinence rate of 18% compared to 9.9% for the NRT group [19]. However, there have been no studies yet comparing e-cigarettes to other tobacco use disorder medications such as bupropion or varenicline.

Pharmacotherapy for tobacco use disorders is relatively limited, with strong evidence only supporting the use of varenicline, bupropion, and NRT in combination with smoking cessation counseling. Varenicline is the most effective monotherapy for tobacco use disorders, with a 1-year abstinence rate of 22-23% [20]. Bupropion has a 1-year abstinence rate of 15-16% [20], and NRT using multiple routes of administration has a 1-year abstinence rate of 7% [21]. A 2017 large multicenter randomized, placebo-controlled trial looked at the efficacy of tobacco use disorder therapies versus placebo for abstinence rates over 24 weeks and found that varenicline was 2.94 times more effective than the placebo. Bupropion and NRT were 1.96 and 1.86 times more effective than placebo, respectively [22]. All of the medications have substantial relapse rates, with some studies showing 12-24-week abstinence rates to be

approximately twice as high as the 1-year rates. It should also be noted that mixed evidence exists for the use of combination therapy of varenicline and bupropion as a potentially superior therapy compared to either as monotherapy based on 1-year abstinence rates [23].

While there is only limited data on the use of e-cigarettes for the long term treatment of tobacco use disorders, it is reasonable to hypothesize that their efficacy would likely be similar to, and possibly superior to, bupropion insofar as 1-year abstinence rates are concerned. Rates could be higher, as other studies have reported that 30.4% of smokers who transitioned to e-cigarettes quit smoking entirely [12], but further research will be needed to elucidate these results fully. Another potential area of focus is determining the best method of transitioning to e-cigarettes, as 54.6% of those who vape also use traditional cigarettes. Conversely, there is a roughly 15% subset of the e-cigarette user population, [12] who were never tobacco users. While the evidence is clear that e-cigarettes are safer than traditional cigarettes, their use should not be encouraged in individuals who are not current tobacco users due to the limited data on the long-term use of these products.

Furthermore, the lack of evidence on the long-term use of pure nicotine should cause additional pause, especially given that e-cigarettes can contain up to 5% [24] nicotine compared to the 1-2% [25] seen in traditional cigarettes. The risks of e-cigarettes have not been conclusively stratified and also offer a mechanism to misuse or abuse compounds containing THC and other additives resulting in life-threatening complications such as VALI. The lack of superior efficacy, limited long term data, and safety concerns surrounding e-cigarettes necessitates further research into alternative therapeutic agents for the treatment of tobacco use disorders. One such agent is psilocybin, which has

shown potential in the treatment of numerous conditions and specifically smoking cessation.

In a small-scale study, 15 patients were given two to three moderate doses of psilocybin over the span of eight weeks in addition to evidence-based cognitive-behavioral therapy (CBT) for smoking cessation. At six months, 80% of the treatment group was abstinent from smoking, with rates decreasing to 66% at one year and 60% at 30 months [26]. These results are encouraging for the long-term treatment of tobacco use disorders insofar as psilocybin offers numerous advantages compared to standard therapy. Psilocybin, when administered in a therapeutic environment under appropriate protocols, is an extremely safe and well-tolerated medication. It, like other classical psychedelics, is nonaddictive, has no known overdose potential, and repeated administration within a short time causes rapid tachyphylaxis at the 5-HT<sub>2A</sub> receptor site [27]. The side effects associated with the use of psilocybin and other psychedelics are generally limited to the duration of the experience. They can include anxiety, panic attacks, nausea, vomiting, diaphoresis, and depersonalization, which can be minimized when taken in therapeutic environments with trained professionals. One significant risk is the exacerbation of underlying severe psychiatric illnesses such as schizophrenia and bipolar disorder, though no evidence suggests that these agents cause severe psychiatric conditions, and long-term data actually suggests that psychedelic use is linked with better psychological health [27]. Rare risks include the potential for vasospasm, adverse drug-drug interactions when used with other psychiatric medications such as selective serotonin reuptake inhibitors, and long-term side effects like Hallucinogen Persisting Perception Disorder [27]. The incidence of all of these risks can be reduced by adequately screening patients

with corresponding risk factors and excluding those individuals from therapy or more thoroughly counseling them on the potential risks. Tobacco users are already at a higher risk of cardiovascular disease and, therefore, should be counseled on the risks before therapy.

The implications of psilocybin for the treatment of tobacco use disorders could be substantial not only from a population health perspective but also from a healthcare economic standpoint. Even assuming a regression toward the mean and conservative estimates, the benefits of a medication that could hypothetically result in a 40-50% 1-year abstinence rate is still approximately twice as effective as the best current pharmacotherapy. The potential cost savings from this level of intervention would be substantial for direct healthcare expenditures. From a patient's perspective, the cost-benefit ratio would significantly favor psilocybin assisted psychotherapy over the current standard of care. Psilocybin eliminates the problems associated with daily medication compliance and the side effects associated with prolonged use of psychotherapeutic medications. Additionally, it has a more favorable pharmacologic profile and shorter total duration of therapy. Lastly, the likely therapeutic effects on other psychiatric conditions is an added benefit. The positive outcomes from small scale studies, prospective economical cost savings due to improved public health standards, and overall favorable safety profile could make psilocybin a revolutionary treatment. It is imperative that more research is done to investigate the use of psilocybin assisted psychotherapy for the treatment of tobacco use disorders.

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