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Time to be blunt: Substance use in cystic fibrosis

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Abstract

Background: As the population of people with cystic fibrosis (pwCF) continues to age, attention is shifting towards addressing the unique challenges teenagers and adults face, including substance use. Changing attitudes and legality regarding marijuana and cannabidiol (CBD) may influence their use among pwCF, but data on the rate of use, reasons for use, and administration methods are lacking.

Objective: Investigate marijuana, CBD, e-cigarette, and cigarette usage among pwCF and explore differences in demographics, disease severity, and cystic fibrosis transmembrane receptor (CFTR) modulator use between recent users and nonusers.

Methods: This cross-sectional study used a one-time electronic survey to assess marijuana, CBD, e-cigarette, and cigarette use in pwCF aged >13 years. Demographic and clinical characteristics were compared between recent users and nonusers. The association between recent substance use and CFTR modulator use was analyzed using logistic regressions.

Results: Among 226 participants, 29% used marijuana, 22% used CBD, 27% used e-cigarettes, and 22% used cigarettes in the last 12 months. Users of all substances were more likely to be college-educated or aged 29–39 years than nonusers. E-cigarette users were 2.9 times more likely

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to use CFTR modulators (95% confidence interval [95% CI]: 0.98–11.00, p = .08) and marijuana users were 2.5 times more likely to use CFTR modulators compared to nonusers, adjusted for confounders. CBD, e-cigarettes, and cigarettes users were more likely to have an abnormal mental health screen compared to nonusers. A high proportion of never-users of marijuana and CBD expressed interest in using.

Conclusion: Substance use is more prevalent among pwCF than previously reported and needs to be addressed by healthcare providers.

Keywords

cannabidiol; cystic fibrosis; e-cigarettes; marijuana; vaping

1 | INTRODUCTION

Over the past decade, there has been a notable change in the consumption patterns of inhaled and ingested substances, driven in part by the increased legalization of cannabis and the growing popularity of electronic cigarettes (e-cigarettes).[1] While cigarette use is on the decline, the use of e-cigarettes and marijuana has witnessed an upward trend, which is expected to continue with the ongoing progress of cannabis legalization across states and diminishing societal stigma.[2] Despite these changes, there remains limited research on the frequency of use, effectiveness, and safety of these substances for various medical conditions, particularly among individuals with underlying lung disease.

Cystic fibrosis (CF), formerly considered a fatal condition, has experienced a remarkable transformation, largely attributed to advances in precision medicine and the introduction of modulator therapy.[3] As the CF population continues to age, attention is shifting towards addressing unique challenges teenagers and adults face, including mental health and substance use. People with CF (pwCF) may seek complementary and alternative treatments to address common issues associated with their chronic illness, including treatment burden, anxiety, depression, decreased appetite, pain, and sleep disturbances.[4,5] Additionally, as health outcomes improve in the era of effective modulator therapy and respiratory symptoms become less prominent, pwCF may resort to inhalation of substances that could have significant impact on their lung health.

Limited data currently exists on the prevalence, modalities, perceptions, demographic, and health factors associated with using marijuana, cannabidiol (CBD), e-cigarettes, and cigarettes in pwCF, particularly in the era of effective modulator therapy. In the past decade, there were only two studies on substance abuse in CF[6,7]; both were conducted before the legalization of marijuana and before the majority of pwCF qualifying for effective modulator therapy. Given these evolving circumstances, it is essential to reexamine substance use and its perception among pwCF. Gaining a deeper understanding of substance usage patterns can enhance the quality of clinical care and provide valuable insights into the underlying reasons, empowering healthcare teams to provide informed guidance and support.

In this study, we investigated the rate of use of marijuana, CBD, e-cigarette, and cigarettes within the CF community and the characteristics of users. We sought to determine if pwCF

using these substances were on cystic fibrosis transmembrane receptor (CFTR) modulators as well. Lastly, we investigated reasons for and attitudes regarding substance usage and self-reported clinical outcomes with substance use.

2 | METHODS

2.1 | Study design

This was a cross-sectional study using a one-time electronic survey about the use of marijuana, CBD, e-cigarettes, and cigarettes among pwCF.

Study recruitment took place from January to May 2022 using various online platforms, including closed membership CF support groups on Facebook, newsletters from the CF Foundation, and CF centers via the CF listserv. The survey was administered through web-based REDcap surveys available in English. No financial incentives were offered. Electronic consent was obtained through implied consent which outlined the study length, principle investigator and purpose of the survey.

2.2 | Subjects

Subjects were included if they were 13 years and older, diagnosed with CF, and residing in the United States.

2.3 | Substance use terminology

Subjects were asked about the substances used, including marijuana, CBD, e-cigarettes, or cigarettes defined in a consistent manner below:

1. Marijuana and CBD products: The cannabis plant contains more than 120 chemical compounds, including delta-9-tetrahydrocannabinol (THC) and CBD. THC is psychoactive and is responsible for the intoxicating effects commonly associated with marijuana use. CBD is a nonpsychoactive compound that has gained popularity for its potential therapeutic effects, including reducing inflammation, pain, and anxiety.[8] Marijuana has THC levels greater than 0.3% and varied levels of CBD. Marijuana included any form, including but not limited to edibles, tinctures, oil, and joints. CBD products have low levels of THC (less than 0.3%) and higher levels of CBD. CBD includes any form, including but not limited to gummies, creams, oils, and pills.

2. E-cigarettes/vaping: E-cigarettes are electronic battery-powered devices containing a liquid that is vaporized and inhaled. It can be referred to as vape pen, hookah-pens, electronic hookahs (e-hookahs), electronic cigars (e-cigars), electronic pipes (e-pipes), or e-vaporizers.

3. Cigarettes: Cigarettes are rolls of finely cut tobacco leaves wrapped in paper that is smoked.

2.4 | Measures

2.4.1 | Substance use frequency—*Recent users* were classified as those who reported using marijuana, CBD, e-cigarettes, or cigarettes within the past 12 months and did not

report quitting. Recent users were asked about frequency of use (daily or almost daily, at least once a week, at least once a month, or less than monthly), reasons for using, and side effects experienced. *Former users* were those who reported previous use of marijuana, CBD, e-cigarettes, or cigarettes but not in the past 12 months. Former users were asked about reasons for quitting. *Never users* were those who never used marijuana, CBD, e-cigarettes, or cigarettes. Never users were asked about their attitudes towards the substance and interest in using them in the future. The *nonuser* group includes both former users and never users.

2.4.2 | Substance use modality—Recent substance users were asked what modality they used overall and more often. Marijuana modalities included smoking (in a joint, bong, pipe, blunt), eating (in brownies, cakes, cookies, candy), drinking (in tea, cola, alcohol), vaporizing (in e-cigarette-like vaporizer), dabbing (using butane hash oil, wax, concentrates), or some other modality. CBD modalities included sublingual, capsules or pills, mouth spray, topical, vaping, smoking, suppository, edibles, drinking, or using some other modality. E-cigarettes are a modality but can contain different mists, including nicotine, marijuana, CBD, only flavoring, or other liquid.

2.4.3 | Reasons for use and side effects—For each substance, recent substance users were asked the reason for use, such as anxiety, fun, appetite stimulant, peer group use. Recent users reported if they use marijuana for medical, recreational, or both reasons. For each substance, subjects reported any positive or negative effects experienced. For each side effect or symptom experienced, subjects rated the severity from much worse to much better. Subjects reported if they experienced weight or lung function changes with use.

2.4.4 | Attitudes towards substances—Never users were given three statements for each substance, including "I would never use no matter what," "I am willing to learn more about the potential benefits and risks," "I am curious about using but have not had the opportunity," and an additional statement specifically for marijuana "I am open to using it if it were legalized." They provided their ratings on a sliding scale, ranging from 0 to 10, which were grouped into five categories ranging from strongly disagree to strongly agree.

2.4.5 | CF disease characteristics—Subjects reported their pancreatic enzyme use, latest forced expiratory volume in 1 s (FEV_1) percent predicted (greater than 80%, between 70% and 79%, between 60% and 69%, below 60%, other, I'm not sure), perceived overall health (poor, fair, good, very good, and excellent), and perceived lung health (poor, fair, good, very good, and excellent). Subjects were asked if they were currently on a CFTR modulator.

2.4.6 | Demographics—Subject demographics included self-identified: age, race/ethnicity (Asian or Pacific Islander, Black or African American, Hispanic or Latino, Native American or Alaskan Native, White or Caucasian, a race or ethnicity not listed here, prefer not to answer), gender (female, male, transgender, nonbinary, prefer to self-describe, and prefer not to answer) state of residence, highest education level achieved (college degree or higher, no college degree) and household income (unsure/not making an income, less than $50,000, $50,000–$99,999, more than $100,000).

2.4.7 | Mental health—Subjects' mental health was assessed utilizing the patient health questionnaire 4 (PHQ-4), which consists of two anxiety and two depression questions. Total score >3 on either the anxiety or depression questions indicated positivity for either of those disorders and was considered an abnormal mental health screen. Scores are rated as normal (0–2), mild (3–5), moderate (6–8), and severe (9–12).

The survey consisted of four sections of questions on each substance (marijuana, cannabidiol, e-cigarettes, and cigarettes), with a total of 110 questions. The survey also included a section which asked subjects about their experiences with their healthcare team. The survey was comprised of branching logic and skip questions. Subjects who reported not using any substance received a minimum of 30 questions to answer. The format of the survey included multiple choice, Likert scale ratings, slider questions, and open-ended questions. The survey was reviewed, and feedback was given by the CF Foundation.

2.5 | Statistical analysis

Survey responses were tabulated and reported as counts and percentages. Recent users were compared to nonusers of each substance for all analyses. To assess differences in socioeconomic characteristics, demographics, and illness severity markers, Fishers exact test was used. Univariate and multivariate logistic regressions were performed to evaluate the unadjusted and adjusted association between usage of CFTR modulators and recent usage of each substance. Potential confounders included in the multivariate models were chosen a priori based on prior literature and a directed acyclic graph of the framework of potential relationships of use of CFTR modulators and substance use. Potential confounders were gender (female, male, and other), age (13–25, 26–39, 40–80 years old), race and ethnicity (non-Hispanic White, Asian/Black/Hispanic/other race), FEV_1 percent predicted (<60%, 60%–79%, >80%), PHQ-4 (normal/mild, moderate/severe). Subjects with missing data were excluded from the regression analyses. A p value of less than .05 was considered statistically significant. All statistical analyses were conducted using R version 4.2.1 (R Foundation for Statistical Computing). The study procedures were reviewed and approved by the Institutional Review Board at the University of California, San Francisco (21–34926).

3 | RESULTS

A total of 264 initiated the survey, with 86% ($n = 226$) meeting inclusion criteria and completing this one-time survey. Recent use was reported by 29% ($n = 66$) of subjects for marijuana, 22% ($n = 49$) for CBD, 27% ($n = 60$) for e-cigarettes, and 22% ($n = 49$) for cigarettes. Only 0.9% ($n = 2$) subjects used all four substances, 6.2% ($n = 14$) used three substances, and 22.6% ($n = 51$) used two of the substances recently (Figure 1).

The frequency of marijuana, CBD, e-cigarette, and cigarette usage varied among those who reported recent use. Daily or near-daily use was highest in users of cigarette (45%, $n = 22$) and e-cigarette (33%, $n = 20$). Marijuana users were more likely to use daily or near-daily (23%, $n = 15$) compared to CBD users (16%, $n = 8$). A total of 39% ($n = 26$) of marijuana users, 33% ($n = 16$) CBD, and 35% ($n = 21$) e-cigarette users had at least once a week usage compared to 22% ($n = 11$) of cigarette users (Figure 2).

Overall, we found that recent users of each of the four substances were more likely to be college-educated, between the ages of 26 and 39 years old, and Black when compared to nonusers. Demographic and socioeconomic characteristics between recent users and nonusers differ depending on the substance used (Table 1). Compared to nonusers, recent users of CBD, e-cigarettes, and cigarettes were more likely to be male, which contrasts with recent marijuana users, who were slightly more likely to identify as female and other gender identities. Black subjects were more likely to be recent users of all substances than other races. Non-Hispanic white subjects were more likely to be recent users of marijuana and cigarettes. Asian, Native American, other races, or multirace subjects were more likely to be recent users of e-cigarettes. It is worth noting that while we did appreciate significance when comparing race/ethnicity to recent substance use, representation of non-White participants was limited, potentially limiting the generalizability of the findings. Specific to marijuana, there was no significant association between recent users and nonusers and state of residence in terms of legality (illegal, medically legal, and legalized) based on cannabis laws during the study period. However among recent users, there was a higher percentage of use in states where marijuana was legalized (73%, $n = 45$), compared to those in medically legal (22%, $n = 14$) and illegal states (5%, $n = 3$).

Significant patterns also emerged with respect to markers of CF disease severity and PHQ-4 scores between recent users and nonusers (Table 2). Recent marijuana users were more likely to be on pancreatic enzymes, while recent cigarette users were less likely to be on pancreatic enzymes. Subjects with self-reported FEV_1 percent predicted of 60%–80% were more likely to be recent users of e-cigarettes and cigarettes as compared to nonusers who were more likely to have a self-reported FEV_1 less than 60% and greater than 80%. There were no differences in pulmonary function between recent users and nonusers of marijuana or CBD (Figure 3).

Recent users of CBD, e-cigarettes, and cigarettes were more likely to have an abnormal mental health screen by PHQ-4 compared to nonusers. CBD users were more likely than nonusers to have a severe score on the PHQ-4, report depressive symptoms on the PHQ-4, but there was no difference in anxiety symptoms. E-cigarette and cigarette users were more likely to have a mild, moderate, and severe score on the PHQ-4 than nonusers, as well as, more likely to report anxiety and depressive symptoms on the PHQ-4. There was no significant difference found in mental health between users and nonusers of marijuana.

There were differences in CFTR modulator use between recent users and nonusers of substances. Recent marijuana users were 1.92 times more likely to report being on CFTR modulators in univariate logistic regression (95% CI: 0.87–4.70, $p = .1$) and 2.45 times more likely in the multivariate logistic model adjusted for age, gender, race, ethnicity, $ppFEV_1$, and PHQ-4 (95% CI: 0.97–7.17, $p = .08$). Recent users of e-cigarettes were 4.07 times more likely to report taking CFTR modulators (95% CI: 1.54–14.07, $p = .01$) in the univariate logistic regression, and 2.92 times more likely in the multivariate analysis adjusted for age, gender, race, ethnicity, $ppFEV_1$, and PHQ-4 (95% CI: 0.98–11.00, $p = .08$). Although the differences for both marijuana and e-cigarettes did not reach statistical significance, the confidence intervals exclude any meaningful differences of lower CFTR modulator use in

recent substance users compared to nonusers. There were no significant differences in recent cigarette or CBD users by CFTR modulator use in logistic regressions (Table 3).

3.1 | Reasons for use

The reasons for use varied across substances, with a common theme of anxiety and social influences (such as friends and family) emerging among the top reasons for use across all four substances. Among marijuana users, sleep disturbance was the most common reason for use, while among CBD users, pain management was the most common reason for use. E-cigarettes were primarily used for flavor experimentation and curiosity, while reasons for cigarette use were stress relief and enjoyment (Table 4). Specific to marijuana, 30% ($n = 20$) of subjects used it for medical reasons, 27% ($n = 18$) for recreational, and 42% ($n = 28$) used it for both.

3.2 | Effects of substance use

Substance users reported various effects, some positive and some negative. Both marijuana and CBD users reported concentration difficulties and energy changes; CBD users mainly noted an improvement in energy, while marijuana users noted increased drowsiness. Appetite changes were frequently reported; many marijuana users reported improved appetite, while many e-cigarette and cigarette users reported decreased appetite. E-cigarette users frequently experience nausea and vomiting. Cough and shortness of breath were often reported by e-cigarette and cigarette users. Despite reporting various effects of substance use, the majority of recent users reported no weight or lung function changes related to their substance use.

3.3 | Quitting substance use

The rates of quitting and the reasons for quitting varied between substances. Former users of marijuana and CBD were more likely to quit than former users of e-cigarettes and cigarettes. Surprisingly, 33% ($n = 32$) formerly used marijuana and 38% ($n = 30$) formerly used CBD, while only 12% ($n = 8$) formerly used e-cigarettes and 22% ($n = 14$) formerly used cigarettes. There were a wide variety of reasons reported for quitting each substance. Among former marijuana users, the primary motivations for quitting were lack of enjoyment (58%, $n = 14$) and a desire to avoid getting high (50%, $n = 12$). While the primary reason cited by former CBD users for quitting was the perception of ineffectiveness (43%, $n = 13$). Health concerns were cited as the predominant factors for quitting among e-cigarette (75%, $n = 6$) and cigarette (71%, $n = 10$) users.

3.4 | Never-users

Many subjects reported never experimenting with any substances, with 56.6% ($n = 128$) having never tried marijuana, 65.0% ($n = 147$) having never tried CBD, 69.9% ($n = 158$) having never tried e-cigarettes, 72.1% ($n = 163$) having never tried cigarettes and 38.5% ($n = 87$) having never tried any of these four substances in their lifetime.

Attitudes varied among those who had never used substances. Subjects who have never used marijuana or CBD displayed less aversion to these substances than those who have never used e-cigarettes or cigarettes. Among never-users, a higher proportion of participants

agreed with the statement, "I would never use no matter what" in relation to e-cigarettes (77%, $n = 122$) and cigarettes (81%, $n = 132$) compared to marijuana (30%, $n = 39$) and CBD (26%, $n = 38$). Many nonusers were curious about using marijuana and CBD; 48% ($n = 61$) of never-users of marijuana and 60% ($n = 88$) of never-users of CBD agreed with the statement, "I am curious about using but have not had the opportunity." In comparison, only a small percentage of never-users of e-cigarettes (8%, $n = 12$) and cigarettes (5%, $n = 8$) agreed with that statement. Many never-users of marijuana (65%, $n = 83$) and CBD 60%, $n = 88$) agreed with the statement, "I do not know enough about this substance, but I am open to learning more about the risks and benefits." In contrast, very few never-users of e-cigarettes (5%, $n = 8$) and cigarettes (3%, $n = 5$) agreed with this statement. More than half of marijuana never-users were interested in trying marijuana if it was legal (52%, $n = 67$).

4 | DISCUSSION

In this cross-sectional study of marijuana, CBD, e-cigarette, and cigarette use in teenagers and adults with CF, we found that a substantial proportion of pwCF engaged in experimentation with at least one of these substances over their lifetime. Surprisingly, approximately one-quarter of subjects surveyed reported recently using either marijuana, CBD, e-cigarettes, or cigarettes, with marijuana and e-cigarettes being the most commonly used substance.

We found notable differences in the rates of marijuana, e-cigarette, and cigarette usage in pwCF compared to prior studies. Our study reports the rates of CBD usage in pwCF for the first time, showing a prevalence of 22% ($n = 49$) among subjects in this study. In a cross-sectional study of teenagers and young adults with CF, Hamberger and colleagues found that 27.4% ($n = 51$) of subjects used marijuana, 15.2% ($n = 51$) used e-cigarettes and 25.7% ($n = 87$) used cigarettes in their lifetime. However, their study did not investigate current or recent usage.[7] In our study, we found a much higher lifetime use of marijuana (43.4%), e-cigarettes (30.1%), and cigarettes (27.9%). We also found a higher rate of usage among recent users than other studies with 29.4% ($n = 66$) of subjects reporting marijuana use in the last year. In contrast, a cross-sectional study of six CF centers found a lower prevalence, with 16.5% reporting marijuana use in their lifetime and 15.4% in the last year.[6] This study by Stephen and colleagues[6] focused on usage and attitudes towards medical marijuana in pwCF, while our study focused on all use of marijuana in pwCF. The higher rate of use of marijuana likely reflected the changing legalization of marijuana in the United States in recent years. The higher usage rates of the other substances in our study also reflected broader trends in substance use in the United States; our data is consistent with national data from the general US population, showing that 43% of Americans used marijuana, 19% vaped nicotine, 22% vaped marijuana, and 19% used cigarettes in the last year.[2]

4.1 | Characteristics of substance users

Our study gathered important information about characteristics of pwCF who use substances that have not been previously reported. Substance use was higher across all substances among pwCF who were college-educated, aged 26–39 years old, or Black. While male pwCF were more likely to be recent users of CBD, e-cigarettes, and cigarettes, pwCF who

are female or have other gender identities were more likely to use marijuana. Interestingly, recent users of e-cigarettes and cigarettes were less likely to have normal or severe lung function compared to nonusers; Recent use of e-cigarettes and cigarettes was higher in those with mild or moderate lung disease. There was no significant difference in pulmonary function by usage of marijuana and CBD. To explain these findings, we hypothesize that individuals with poorer lung function have increased health care interactions and therefore may be better educated on the risks of vaping, while those with higher lung function may be more health conscious and exhibit higher health awareness. It is important to note that while our study identified important demographic and health characteristics associated with various substance use in pwCF, the prevalence of substance use overall was high in our study. Our findings confirmed the importance of incorporating substance use discussions and education into routine care regardless of demographic, health, or socioeconomic status.

4.2 | Substance modalities

We observed a high usage rate of marijuana vaporization and smoking, and a surprisingly high utilization of inhalational methods for CBD. CBD is often less frequently asked about among CF healthcare teams, and many CF care providers feel unprepared to answer questions regarding CBD.[9] Given the potential for worsening lung disease and respiratory symptoms,[10] it is vital to routinely discuss both marijuana and CBD usage, counsel, and discuss modalities. Inhaling any substance can exacerbate airway inflammation and hasten lung damage, especially in those already afflicted with underlying lung disease.[9] Furthermore, alternative forms of marijuana and CBD, such as edibles and topical solutions, present challenges due to their higher cost,[11] limited accessibility,[12] and potential interactions with CFTR modulator drugs,[13] thereby potentially complicating their usage as an alternative to CF management strategies.

4.3 | CFTR modulators and substance use

With significant improvements in lung and overall health with highly effective modulator therapy, we investigated the rate of use of substances in pwCF on CFTR modulators. We found that e-cigarette and marijuana use were more than two times higher in those on CFTR modulators than those not on CFTR modulators. Although these associations did not reach statistical significance after adjusting for other factors, these associations are likely clinically meaningful as there was a strongly positive trend of the odds ratio, and essentially rule out that pwCF on CFTR modulators have lower substance use. There were no significant differences in CBD and cigarette use between those on and not on CFTR modulators. The increased trend in e-cigarette and marijuana use among those on CFTR modulators poses significant concerns as there is ample data on lung injuries associated with e-cigarettes.[14] Tobacco smoke exposure can cause impairment in CFTR functional expression, which may mitigate the benefit of CFTR modulators.[14] The impact of marijuana smoke exposure on CFTR expression has not been studied. With social influence and increased access to these agents, it is critical that drug use assessment and education be implemented in routine CF care, especially as pwCF live longer in the era of effective modulator therapy to prevent adverse outcomes from substance use.

4.4 | Untreated symptoms

Mental health continues to be a major concern in pwCF.[15,16] In our study, many subjects had abnormal mental health screens; except for marijuana, poor mental health was associated with recent substance use. Notably, recent e-cigarette and cigarette users were associated with anxiety and depression, while recent CBD users were associated with depressive symptoms. Many reported using substances to minimize the impact of their illness and improve their mental well-being, often to address anxiety, depression, and sleep issues. Recent users frequently used CBD and marijuana as mood stabilizers; however, hyperawareness and anxiety were also reported as side effects. Approximately half of subjects who quit marijuana reported wanting to avoid psychoactive effects. Although recent users noted worsening mental health with e-cigarettes and cigarettes and a desire to stop using, quitting rates were lower when compared to marijuana and CBD, likely due to the highly addictive nature of nicotine.[17] While the causal relationship between substance use and mental health remains uncertain, it is crucial to recognize that some substances can exacerbate pre-existing mental health issues frequently observed in patients with chronic diseases.[18] It is also worth noting that some patients may experience neurocognitive, mood, and anxiety changes after initiating CFTR modulator therapy. Our study did not explore the relationship between modulator therapy initiation, substance use timing and mood which may be a confounding factor.

4.5 | Risk for increased use in CF population

Similar to findings reported by Stephen and colleagues,[6] wealso found that approximately half of the subjects who had never used would try marijuana or CBD if given the opportunity or if marijuana was legal. This can indicate a probable increase in substance usage among the CF community as societal stigma around marijuana decreases and legality continues to shift. In addition, we found that many pwCF used substances due to the influence of friends and family and seeking a sense of normalcy, as seen in a prior study.[19] As pwCF are leading longer lives with fewer significant health disruptions due to CFTR modulators, substance use prevalence may increase over time.

There is a great need to expand the current knowledge of and guidance regarding marijuana and CBD use in the CF patient population. Further research is warranted to counsel pwCF accurately, as many report experiencing therapeutic benefits. With the advancements in therapies that enhance the quality of life and increase life expectancy, coupled with evolving legal landscapes, pwCF will have more opportunities to explore these substances than previous generations.

In this study, we have identified several factors with respect to substance use in pwCF that merit further consideration in CF routine patient care and future research. Most importantly, CF care providers must screen for substance use starting in the patient's early teenage years. Second, CF care providers should feel comfortable addressing the topics of marijuana, CBD, e-cigarettes, and cigarette use and potential risks with patients and families. Finally, more studies are needed to understand potential interactions between these substances, especially marijuana and CBD and the concomitant use of CFTR modulators.

4.6 | Study limitations

There are a few limitations to our study. First, we relied on self-reported rather than clinical data, so the associations of substance use with health outcomes and CFTR modulators may be under- or over-reported. Second, the survey was administered through online channels utilizing social media platforms, a method susceptible to infiltration of fraudulent responses. We addressed this by including internal validity questions and using Completely Automated Public Turing test to tell Computers and Humans Apart feature. We carefully reviewed the validity questions and removed suspected automated responses by bots from the study. Third, subjects recruited via social media may represent pwCF who have an interest in these substances, which would potentially overestimate the rate of use, however, we found that it was not significantly skewed toward recent use relative to nonuse. The survey was also not translated into Spanish, limiting the participation of a subset of potential subjects, and our findings' generalizability; therefore, our results should not preclude discussions around substance use in all pwCF.[20]

5 | CONCLUSION

Our study demonstrated an increased trend for all substance uses in pwCF. As e-cigarettes become more popular and more states legalize marijuana for medical and recreational use, it will become crucial to establish consistent guidelines, screening tools, and enhanced research efforts to understand potential health risks and benefits specific to this population. CF healthcare teams should routinely counsel their patients regarding substance use.

ACKNOWLEDGMENTS

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations:

CBD	cannabidiol
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane receptor
CI	confidence interval
COVID-19	coronavirus-19

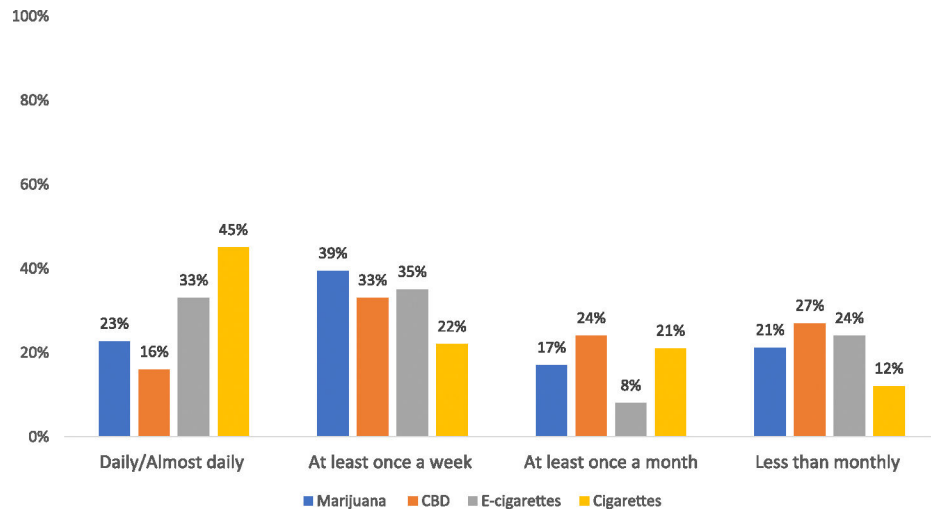| **FEV$_1$** | forced expiratory volume in the first second |
PHQ-4	patient health questionnaire 4
PwCF	people with cystic fibrosis
THC	delta-9-tetrahydrocannabinol

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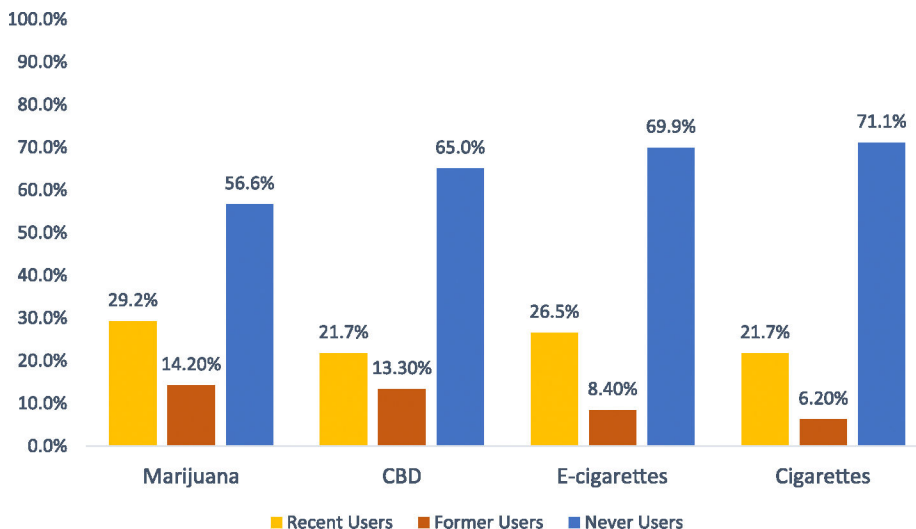
FIGURE 1.

Substance use in people with cystic fibrosis. Recent users were characterized as those who have used these substances in the last 12 months and did not indicate quitting. Former users were characterized as those who have not used in the last 12 months and/or indicated quitting. Never users were characterized as those who have never used the substance in their lifetime. CBD, cannabidiol; E-cigarettes, electronic cigarettes.

FIGURE 2.
Frequency of substances in recent users in people with cystic fibrosis (CF). CBD, cannabidiol; E-cigarettes, electronic cigarettes.
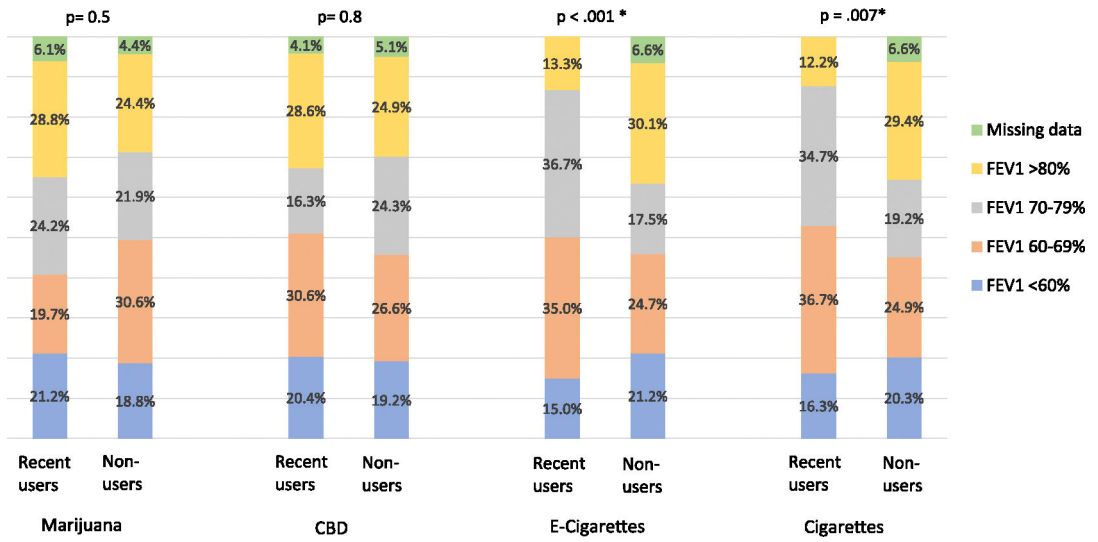
FIGURE 3.
Self-reported forced expiratory volume in one second (FEV$_1$) of recent users compared to nonusers. CBD, cannabidiol; E-cigarettes, electronic cigarettes.

TABLE 1

Characteristics of recent marijuana, cannabidiol, e-cigarette and cigarette users and nonusers.

	Marijuana			Cannabidiol			E-cigarettes			Cigarettes		
	Recent	Nonuser	p value	Recent	Nonuser	p value	Recent	Nonuser	p value	Recent	Nonuser	p Value
Number (%)	66 (29.2%)	160 (70.8%)		49 (21.7%)	177 (78.3%)		60 (24.4%)	166 (73.5%)		49 (21.7%)	177 (78.3%)	
Gender			.2			.4			.048*			.3
Female	34 (51.5%)	82 (51.3%)		22 (44.9%)	94 (53.1%)		23 (38.6%)	93 (56.0%)		20 (40.8%)	96 (54.2%)	
Male	27 (40.9%)	72 (45.0%)		24 (49.0%)	75 (42.4%)		35 (58.3%)	64 (38.6%)		26 (53.1%)	73 (41.2%)	
Other	5 (7.6%)	1 (0.6%)		3 (6.1%)	5 (2.8%)		2 (3.3%)	6 (3.7%)		2 (4.1%)	6 (3.4%)	
Missing	0 (0%)	5 (3.1%)		0 (0%)	3 (1.7%)		0 (0%)	3 (1.8%)		1 (2.0%)	2 (1.1%)	
Age (years)			.7			.3			.001*			.04*
13–25	18 (27.3%)	45 (28.1%)		10 (20.4%)	53 (29.9%)		22 (36.7%)	41 (24.7%)		14 (28.6%)	49 (27.7%)	
26–39	32 (48.5%)	69 (43.1%)		27 (55.1%)	74 (41.8%)		32 (53.3%)	69 (41.6%)		28 (57.1%)	73 (41.2%)	
40–80	16 (24.2%)	46 (28.8%)		12 (24.5%)	50 (28.2%)		6 (10.0%)	56 (33.7%)		7 (14.3%)	55 (31.1%)	
Race/ethnicity			.4			.6			.005*			.6
Asian, Native American, other races	3 (4.5%)	13 (8.1%)		3 (6.1%)	13 (7.3%)		5 (8.3%)	11 (6.6%)		3 (6.1%)	13 (7.3%)	
Black	6 (9.1%)	9 (5.6%)		5 (10.2%)	10 (5.6%)		8 (13.3%)	7 (4.2%)		5 (10.2%)	10 (5.6%)	
Hispanic	2 (3.0%)	14 (8.8%)		2 (4.1%)	14 (7.9%)		2 (3.3%)	14 (8.4%)		5 (10.2%)	11 (6.2%)	
Non-Hispanic White	53 (80.3%)	120 (75.0%)		37 (75.5%)	136 (76.8%)		42 (70.0%)	131 (78.9%)		35 (71.4%)	138 (78.0%)	
Multirace	2 (3.1%)	4 (2.5%)		2 (4.1%)	4 (2.3%)		3 (5%)	3 (1.8%)		1 (2.0%)	5 (2.8%)	
Education			.5			.8			.2			.4
No college	35 (53.8%)	98 (59.0%)		17 (34.7%)	71 (40.1%)		18 (30.0%)	70 (42.2%)		17 (34.7%)	71 (40.1%)	
College	30 (46.3%)	58 (34.9%)		31 (63.3%)	102 (57.6%)		40 (66.7%)	93 (56.0%)		30 (61.2%)	103 (58.2%)	
Missing	1 (1.5%)	4 (2.4%)		1 (2.0%)	4 (2.3%)		2 (3.3%)	3 (1.8%)		2 (4.1%)	3 (1.7%)	

Note:

*
denotes statistical significance ($p < .05$).

TABLE 2

Health characteristics of recent marijuana, cannabidiol, e-cigarette and cigarette users compared to nonusers.

	All subjects	Marijuana Recent user	Marijuana Nonuser	Marijuana p Value	Cannabidiol Recent user	Cannabidiol Nonuser	Cannabidiol p Value	E-Cigarettes Recent user	E-Cigarettes Nonuser	E-Cigarettes p Value	Cigarettes Recent user	Cigarettes Nonuser	Cigarettes p Value
Number (%)	226 (100%)	66 (29.2%)	160 (70.8%)		49 (21.7%)	177 (78.3%)		60 (26.5%)	166 (73.5%)		49 (21.7%)	177 (78.3%)	
Pancreatic enzyme				.07			.9			.2			.9
Yes	166 (73.5%)	53 (80.3%)	113 (70.6%)		36 (73.5%)	130 (72.4%)		41 (68.3%)	125 (75.3%)		35 (71.4%)	131 (74.0%)	
No	48 (21.2%)	8 (12.1%)	40 (25.0%)		10 (20.4%)	38 (21.5%)		13 (21.7%)	35 (21.1%)		11 (22.4%)	37 (20.9%)	
Missing	12 (5.3%)	5 (7.6%)	7 (4.4%)		3 (6.1%)	9 (5.1%)		6 (10.0%)	6 (3.6%)		3 (6.1%)	9 (5.1%)	
Body mass index				.5			.4			.6			.4
Underweight	48 (21.2%)	10 (15.2%)	38 (23.8%)		8 (16.3%)	40 (22.6%)		16 (26.7%)	32 (19.3%)		14 (28.6%)	34 (19.2%)	
Average weight	112 (49.6%)	34 (51.5%)	78 (48.8%)		22 (44.9%)	90 (50.8%)		27 (45.0%)	85 (51.2%)		20 (40.8%)	92 (52.0%)	
Overweight	59 (26.1%)	20 (30.3%)	39 (24.4%)		17 (34.7%)	42 (23.7%)		15 (25.0%)	44 (26.5%)		14 (28.6%)	45 (25.4%)	
Missing	7 (3.1%)	2 (3.0%)	5 (3.1%)		2 (4.1%)	5 (2.8%)		2 (3.3%)	5 (3.0%)		1 (2.0%)	6 (3.4%)	
Perceived lung health				.4			.3			.8			.7
Poor/fair	93 (41.3%)	25 (37.9%)	68 (42.5%)		16 (32.7%)	77 (43.5%)		23 (38.3%)	70 (42.2%)		22 (44.9%)	71 (40.1%)	
Good/excellent	129 (57.1%)	41 (62.1%)	88 (55.0%)		32 (65.3%)	97 (54.8%)		36 (60.0%)	93 (56.0%)		26 (53.1%)	103 (58.2%)	
Missing	4 (1.8%)	0 (0%)	4 (2.5%)		1 (2.0%)	3 (1.7%)		1 (1.7%)	3 (1.8%)		1 (2.0%)	3 (1.7%)	
FEV_1 % predicted				.5			.8			<.001 *			.007 *
<60%	44 (19.5%)	14 (21.2%)	30 (18.8%)		10 (20.4%)	34 (19.2%)		9 (15.0%)	35 (21.2%)		8 (16.3%)	36 (20.3%)	
60%–69%	62 (27.4%)	13 (19.7%)	49 (29.5%)		15 (30.6%)	47 (26.6%)		21 (35.0%)	41 (24.7%)		18 (36.7%)	44 (24.9%)	
70%–80%	51 (22.6%)	16 (24.2%)	35 (21.1%)		8 (16.3%)	43 (24.3%)		22 (26.7%)	29 (17.5%)		17 (34.7%)	34 (19.2%)	
>80%	58 (25.7%)	19 (28.8%)	39 (23.5%)		14 (28.6%)	44 (24.9%)		8 (13.3%)	50 (30.1%)		6 (12.2%)	52 (29.4%)	
Missing	11 (4.9%)	4 (6.1%)	7 (4.2%)		2 (4.1%)	9 (5.1%)		0 (0%)	11 (6.6%)		0 (0%)	11 (6.6%)	
PHQ-4				.7			.007 *			<.001 *			<.001 *
Normal	74 (32.7%)	19 (28.8%)	55 (34.4%)		8 (16.2%)	66 (37.3%)		6 (10.0%)	68 (41.0%)		6 (12.2%)	68 (38.4%)	
Mild	73 (32.3%)	23 (34.8%)	50 (31.2%)		21 (42.9%)	52 (29.4%)		21 (35.0%)	52 (31.3%)		20 (40.8%)	53 (29.9%)	
Moderate	64 (23.9%)	19 (27.3%)	45 (28.1%)		13 (26.5%)	50 (28.2%)		27 (45.0%)	36 (21.7%)		15 (30.6%)	48 (27.1%)	
Severe	16 (7.1%)	6 (9.1%)	10 (6.2%)		7 (14.3%)	9 (5.1%)		6 (10.0%)	10 (6.0%)		8 (16.3%)	8 (4.5%)	

Note:

*
denotes statistical significance ($p < .05$).

TABLE 3

Unadjusted and adjusted association between usage Of CFTR modulators and substance usage.

	Marijuana		CBD		E-cigarettes		Cigarettes	
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
CFTR modulator use	1.92 (0.87–4.70)	2.45 (0.97–7.17)	1.01 (0.46–2.41)	1.00 (0.42–2.62)	4.07(1.54–14.07)	2.92 (0.98–11.00)	2.32 (0.93–7.08)	1.61 (0.59–5.17)
Gender								
Male (vs. Female)	–	0.85 (0.43–1.63)	–	1.33 (0.65–2.71)	–	3.08 (1.47–6.69)	–	2.10 (1.0–4.56)
Other (vs. Female)	–	4.31 (0.95–23.1)	–	2.10 (0.40–9.60)	–	0.86 (0.11–4.81)	–	1.07 (0.14–5.68)
Race & Ethnicity								
Non-Hispanic White (vs. Asian, Black, Hispanic, Other)	–	1.85 (0.79–4.74)	–	1.06 (0.46–2.60)	–	0.91 (0.39–2.17)	–	1.03 (0.45–2.49)
Age								
26–39 years (vs. <25 years)	–	1.11 (0.52–2.42)	–	1.89 (0.81–4.65)	–	1.35 (0.61–3.09)	–	1.00 (0.86–4.88)
>40 years (vs. <25 years)	–	0.98 (0.39–2.44)	–	1.29 (0.47–3.60)	–	0.23 (0.07–0.68)	–	0.60 (0.19–1.76)
FEV1								
60–79% (vs. <60%)	–	0.64 (0.28–1.48)	–	0.76 (0.31–1.89)	–	2.51 (0.98–7.10)	–	2.05 (0.82–5.67)
>80% (vs. <60%)	–	1.01 (0.41–2.52)	–	1.21 (0.46–3.29)	–	0.72 (0.21–2.49)	–	0.59 (0.17–2.03)
PHQ4								
Mod/Severe (vs. Nl/Mild)	–	1.35 (0.66–2.74)	–	1.60 (0.75–3.41)	–	1.84 (0.88–3.83)	–	1.24 (0.59–2.62)

Note: Marijuana 87.5% of users are on modulators compared to 78.5% of nonusers (*p* = .1). CBD 81.2% of users are on modulators compared to 81.0% of nonusers (*p* = 1.0). Vapiniig 93.1% of users are on modulator compared to 76.8% of nonusers (*p* = .006).

TABLE 4

Reasons for use for marijuana, CBD, e-cigarettes and cigarettes among current users.

	Marijuana $n = 66$	CBD $n = 49$	E-cigarettes $n = 60$	Cigarettes $n = 49$
Anxiety	40 (60.6)	17 (34.7)	30 (50.0)	8 (16.3)
Appetite	19 (28.8)	5 (10.2)	8 (13.3)	5 (10.2)
Arthritis	9 (13.6)	8 (16.3)		
Concentration				19 (38.8)
Crave it	0 (0.0)	0 (0.0)	23 (38.3)	19 (38.8)
Curiosity/try something new	5 (7.6)	7 (14.3)	16 (26.7)	0 (0.0)
Depression	28 (42.4)	10 (20.4)	0 (0.0)	
Energy	0 (0.0)	8 (16.3)	6 (10.0)	8 (16.3)
For fun	24 (36.4)	10 (20.4)	10 (16.7)	23 (46.9)
For the flavor			18 (30.0)	17 (34.7)
Friends/family use it	8 (12.1)	10 (20.4)	4 (6.7)	30 (61.2)
I like the way it makes me feel	24 (36.4)	10 (20.4)	5 (8.3)	28 (57.1)
Migraines	10 (15.1)	8 (16.3)		
Nausea	13 (19.7)	4 (12.2)		
Pain	22 (33.3)	17 (34.7)		
Relaxation/destress	26 (39.4)	14 (28.6)	26 (43.3)	28 (57.1)
Sleeping difficulties	30 (45.4)	5 (10.2)		
Cut down on number of cigarettes			16 (26.7)	
Help quit smoking			12 (20.0)	
Less expensive than smoking cigarettes			8 (13.3)	

Note: areas that were left blank were not specifically asked for that substance.

Abbreviations: CBD, cannabidiol; E-cigarettes, electronic cigarettes.