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Methods and applications in addiction psychiatry research: 2021

Edited by
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Methods and applications in addiction psychiatry research: 2021

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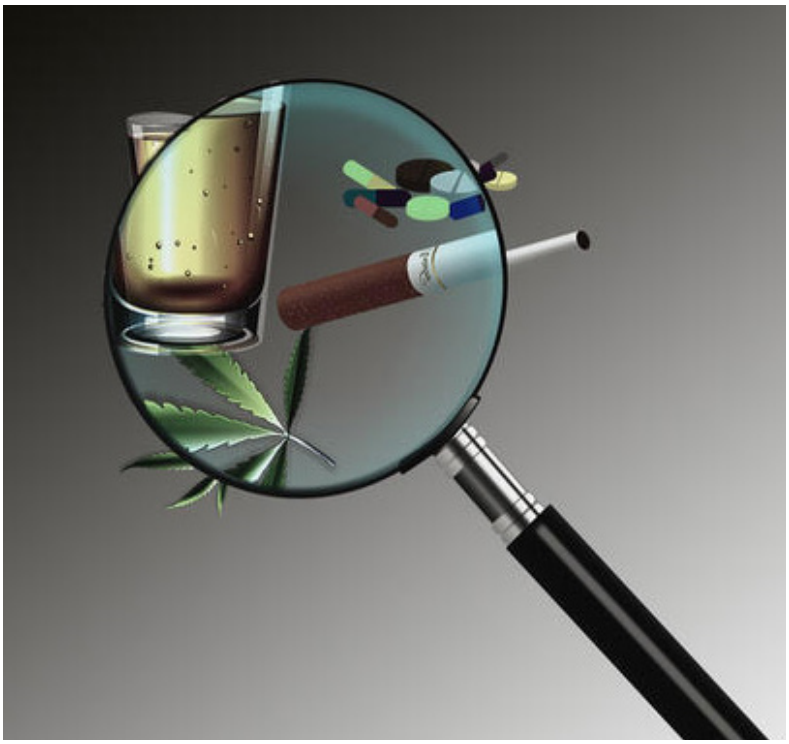

The Topic Editors would like to acknowledge Venere Rotelli for creating the introductory image “Look beneath the surface”.

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Editorial: Methods and applications in addiction psychiatry research: 2021

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Editorial on the Research Topic
Methods and applications in addiction psychiatry research: 2021

Addiction psychiatry research is currently in a continuous developmental stage and it is a field in medicine where the diseases to be studied keep growing in number. Nicotine addiction, cannabis use disorder (CUD), online gambling, or alcohol use disorder are a few examples (1).

In this Research Topic, we highlighted some of the current challenges and advances in this field. We tried and approached the entire landscape by underscoring the point that progress is being made in different aspects to help us deal with addictions better as a system. We included insights about novel and promising approach.

One of the points emerged in the Research Topic was the treatment of the nicotine addiction.

Historically, the treatment of nicotine addiction has been given a low priority in the overall field of addiction, compared with other substance use disorders. Both genetic and environmental are the risk factors for the smoking and subsequent tobacco addiction and many smokers are ambivalent about quitting smoking (2). The systematic review by Vanderkam et al. analyzes the duration of the efficacy of electronic cigarettes containing nicotine on smoking cessation. They found highlighting that abstinence at the end of the intervention was higher in the nicotine electronic cigarette group, compared to nicotine replacement therapy. Different study protocols have also been proposed. Indeed, Hawes et al. aimed at increasing nicotine replacement therapy adherence and smoking cessation among groups of individuals with high smoking rates and low rates of pharmacotherapy use such as those involved in the criminal legal system. Zamboni, Campagnari et al. investigate the potential role of the safe and low-cost drug cytisine to treat nicotine addiction. They compare the effects of combining cytisine with nirdosh, a herbal tobacco substitute, to cytisine only in two groups of patients also undergoing exposure to different virtual reality (VR) settings.

For instance, VR is experiencing an increased used for the assessment, diagnosis and treatment of mental diseases. VR is a computer-generated simulation of the three-dimensional environment with which it is possible to interact in a ostensibly real way (3). In this regard, Wen et al. propose the protocol for a randomized, double-blind, parallel group trial to investigate the effectiveness of transcranial magnetic stimulation (TMS) treatment after VR retrieval in reducing self-reported craving of metamphetamine and drug-related cue reactivity. A VR study protocol is proposed by Giordano et al. too, where they assess the ability of a psychological treatment to treat gambling disorder based on the combination and integration of VR cue exposure therapy and traditional cognitive behavioral therapy, thus proposing a virtual game designed for purposes other than entertainment.

Another point highlighted in the Research Topic is the treatment of CUD which is defined as the impotence to stop consuming cannabis even when it is causing physical or psychological harm. Currently, no effective pharmacological approaches for CUD are available (4). A non-randomized, open-label pilot study conducted by Cleirec et al. assesses the potential of cannabidiol [CBD, the main non-addictive cannabis compound (5)] inhaled using a vaping device in CUD. At the end of the follow-up, 6 users reduce the cannabis consumption by at least 50%., It also demonstrates that people with CUD can use an electronic cigarette as a tool to reduce their cannabis use. Moreover, Ramaekers et al. propose a perspective article highlighting the effect of acute Δ9-tetrahydrocannabinol (THC, the main psychotropic compound of cannabis) in neuroadaptative changes in chronic cannabis users. Their approach includes the quantification of neurochemical and functional brain network alterations in response to an acute THC administration. A randomized, double-blind clinical study conducted by Theunissen et al. attempts to compare the psychoactive effects of natural cannabis (THC) and JWH-018, a synthetic cannabinoid exerting psychotropic effects. The authors find that both drugs impair psychomotor and divided attention with no significant differences between the two drugs. These effects are coupled to psychotomimetic effects, even though dissociative effects are higher for JWH-018, compared to THC.

Benzodiazepines (BDZ) are the first-choice drugs used for the treatment of sleep disturbances and, in some cases, anxiety disorders (6). Zamboni, Portoghese et al. conduct a study to evaluate dependence to high BDZ doses in an Italian sample of 1,354 participants in which they investigate to which extent participants use also other substances such as tobacco, cannabis, alcohol, cocaine and heroin. The authors perform class analysis to identify the use patterns of these drugs. They divided the participants in 3 classes, finding that: participants in class 1 are mostly characterized by young men with the highest probability of using cocaine and alcohol; participants of class 2 are mostly subjects with the highest probability of being former cocaine, THC, heroin and alcohol users; the class 3 is mostly represented by women BZD users.

It has been demonstrated that chronic alcohol produce o cognitive impairements (7). Si et al. overviews how an anti-saccade task can be used as a tool to study the cognitive dysfunctions related to alcohol consumption. Also, authors propose this anti-saccade task for the early detection of relapsing risk of alcohol dependence.

The past decades have experienced the interest in the etiology of substance use disorder and addiction. Several theories highlight that addiction depends not only on alterations in neurobiological and psychological reward mechanisms, but also on the effort to cope with negative emotional experiences. In this context, Feingold and Bitain propose a clinical approach which addresses these aspects to discuss benefits for clinicians and patients working with and through addiction. Moreover, a research article proposed by Santos de Pascual et al. aims to investigate the efficacy of a multimodal treatment for a certain addict population. Their data indicate that changes occur in individuals with drug use during treatment which is also correlated to the complex social reality which is the cause of suffering to people and their relatives.

In conclusion, aware that we are still skimming just the surface of very complex phenomena, further research directions in addiction psychiatry must be specifically implemented. We need to try and better investigate the preventive potential of tools aiming at controlling and limiting substance use disorders. Finally, specific measures must be developed toward new and non-substance-related addictions whose needs are still largely unmet.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

MC has been a consultant/advisor to GW Pharma Limited, GW Pharma Italy SRL and F. Hoffmann-La Roche Limited, outside of this work.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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ORIGINAL RESEARCH
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Polysubstance Use Patterns Among High Dose Benzodiazepine Users: A Latent Class Analysis and Differences Between Male and Female Use

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Benzodiazepines (BZDs) represent one of the most widely used groups of pharmaceuticals, but if used for long periods of time they are associated with dependence and an increased risk of harmful effects. High-dose (HD) BZD dependence is a specific substance use disorder associated with a poor quality of life. It is especially important to pinpoint differences in HD BZD addict subgroups in order to tailor treatment to the individual's specific needs, also considering possible comorbidities with other substance use disorders. We conducted a study to evaluate HD BZD dependence (converted doses to diazepam equivalents, mg) in an Italian sample of 1,354 participants. We also investigated if and to which extent participants co-used other substances (alcohol, tobacco, cannabis/cannabinoids, cocaine, and heroin). We then performed latent class analysis (LCA) to identify the use patterns of these substances, finding three classes: participants in Class 1 (4.3% of the sample) had the highest probability of also using cocaine and alcohol (Polysubstance BZD users); Class 2 comprised subjects with the highest probability of being former heroin, cocaine, THC, and alcohol users (Former polysubstance BZD users); Class 3 represented mono-dependence BZD users (78.5% of the sample) and was the most prevalent among women, while young men were most prevalent in Class 1.

The present study underlines different characteristics in HD BZD users both concerning other addictions and sex, and also highlights the need for a stricter control of BZD use, ranging from prescriptions to sales.

Keywords: benzodiazepine, addiction, latent class analysis, polyabusers, anxiety

INTRODUCTION

Benzodiazepines (BZDs) are among the most commonly prescribed medications for insomnia and anxiety and are extensively used in clinical practice. BZDs act as positive allosteric modulators of the GABA-A (Gamma-Aminobutyric Acid Type A) receptor (1). A number of studies have evidenced that benzodiazepines should be considered a suitable treatment for specific clinical situations and for short-term use only (2–4): indeed, long-term use of this class of drugs increases the likelihood of adverse effects and dependence and should therefore be implemented with caution. Alternative short or intermittent treatments could have important benefits for patients and should be taken into consideration when deciding on a specific course of treatment (5).

Long-term BZD users range from 6 to 76% of total users. Fifteen to forty four percent of them present moderate-to-severe withdrawal symptoms, and 3–4% show a dependence (6).

High-dose (HD) BZD dependence is considered a specific substance use disorder (7) and it consistently reduces quality of life in patients that suffer from it (8, 9). Ohayon and Lader (10) conducted a cross-sectional survey in various European countries (France, Germany, and Italy) and in the UK, and found that an estimated 0.14% of the general population took higher-than-recommended doses of anxiolytic medications, while 0.06% reportedly abused hypnotics (10). These numbers are in line with the 0.16% of high-dose BZD users reported in Switzerland (11) and point toward HD BZD abusers being around 1.5 million in Europe and 600,000 in the United States.

Long-term BZD use was reported to be associated with abnormalities in cognitive functions, including attention, memory and learning, a higher risk of delirium, cognitive decline and accidents (12–21).

BZD withdrawal in patients is an especially discomforting experience. To alleviate withdrawal symptoms, therapeutic strategies such as gradual tapering of the dosage or substituting the target BZD with an equivalent dose of another long-acting benzodiazepine and then tapering have been developed (22, 23).

BZDs have been reported to be secondary drugs of abuse for most individuals, and a much smaller number report BZDs as the primary drugs of abuse. BZD abuse is mainly associated with opioids (54.2%) and alcohol (24.7%) abuse. As reported by Schmitz (24) in her recent review, about 1 in 5 people who abuse alcohol also abuse benzodiazepines (25).

In the last decade, research has been increasingly focused on patterns of polyabuse defined as the use of more than one drug during a specific time period. While patterns of use and characteristics of polyabusers have been examined among many substance users (such as alcohol, cocaine, heroin, etc.), not much is known about polyabuse patterns among BZD abusers. Several studies have aimed to address this complexity by identifying homogenous subgroups of patients who have similar outcomes (26, 27). The same pre-existent characteristics of the patients, indeed, do not consistently produce the same effects.

Understanding the distribution and determinants of polysubstance use is crucial for planning overdose prevention programs and policies. The problem of polydrug use has also been acknowledged as crucial in the context of treatment. There is general consensus that the effects of combining multiple substances of abuse are often problematic to predict and can increase the risks of accidents, overdose and death (28). In this respect, the last 15 years have seen an increased focus on person-centered methodologies that statistically uncover subpopulations with distinct combinations of polysubstance use (29, 30). Latent Class Analysis (LCA) is a type of finite mixture model that is used to identify and describe homogenous subgroups within a heterogeneous population based on the similarity of their response patterns (31). This method has been widely used in previous studies to examine substance use patterns (32–35).

LCA has been used in other studies to identify subgroups of substance use, misuse and addiction, e.g. to tobacco, internet etc. (36–40); notably, it has been used to differentiate problematic alcohol users from addicted users (41).

Regarding BZD addiction, LCA has been utilized by Votaw et al. (42) in a general population sample. In their study, the authors identified three distinct latent classes: limited polysubstance use class, binge alcohol and cannabis use class, and opioid use class.

However, to the best of our knowledge, the present study is the first to examine polysubstance use patterns among individuals who use BZDs as their primary drugs of choice in order to identify different classes of BZD users characterized by distinct substance combinations emerging from LCA.

METHODS

Participants

All participants were in treatment for BZD detoxification at the Addiction Unit of the Verona University Hospital in Verona (Italy). During the study period (November 2003 to February 2020) 1,354 people were screened at the Addiction Unit of the Department of Internal Medicine at the Verona University Hospital for high-dose BZD dependence. Inclusion criteria were: being over 18 years of age; meeting the DSM-IV (43) criteria for benzodiazepine dependence, with more than 6 months' use; high dose benzodiazepines use (HDU). The DSM-IV criteria was applied by the clinician.

All patients also had to have so-called problematic use, defined by either mixing BZDs, escalating dosage, and/or using BZDs for recreational purposes (8, 9, 44). In accordance with previous literature (45, 46), the proposed detoxification program they enlisted in consisted in a 7-day continuous slow infusion of flumazenil (FLU-SI) in an inpatient setting, followed by interventions such as counseling, cognitive-behavioral therapy, and pharmacological therapy to prevent BZD relapse.

Patient demographics, the type of BZD they used and what it had been prescribed for, the duration of its use and its mean daily dose in the previous 3 months, its preferred administration route, comorbid abuse of other substances or other psychiatric disorders and detoxification attempts were assessed upon admission to our Unit.

The definition of what constitutes a "high dose" is still controversial and no real consensus exists about the appropriate clinical criteria that should be applied; in our study, we

recommended inpatient treatment if a patient's BZD intake was at least 5 times higher than the maximum defined daily dose (DDD). Among the BZDs considered, we also included so-called Z-drugs. BZD use was quantified as standardized as diazepam dose equivalents.

The study was conducted according to the Declaration of Helsinki. Its protocol was approved by the ethics committee of the Verona University Hospital (approval code 683CESC) and fully adhered to its guidelines. Patients and controls gave written informed consent to participate in the study and to receive off-label administration of flumazenil (patients only).

Measures

Participants were asked questions regarding their demographic profile, including sex, age, age of first use, education, marital status, and employment status. BZD dependence duration was considered by converting doses to diazepam equivalents (DDDE, mg) (47) and calculating the mean diazepam dose/day.

Furthermore, participants' history of drug addiction and simultaneous drug use was assessed, considering alcohol, tobacco, cannabis/cannabinoids, amphetamines/methamphetamines, barbiturates/sedatives, cocaine, and heroin. To better quantify these variables, we assigned the following: (0) no drugs/alcohol used in the past 12 months, (1) previous history of drug/alcohol addiction, (2) addicted.

Information on these variables was mainly obtained from medical records. DDDE data were based on self-report.

Data Analysis

LCA was implemented to identify the use patterns of seven substances (other than BZDs): alcohol, tobacco, cannabis/cannabinoids, cocaine, and heroin. As the usage rate of amphetamines/methamphetamines and barbiturates/sedatives was low, we removed them from the analyses. LCA including one to six latent classes was estimated by employing the robust maximum-likelihood estimator (MLR) MPlus 7. The LCA was conducted by using 5,000 random sets of start values and 1,000 iterations, and the 500 best solutions were retained for final stage optimization (48, 49). In deciding how many classes should be retained, we considered the statistical appropriateness and consistency with respect to the theoretical meaning and conformity of the extracted classes (50–53).

Different information criteria (IC)-based fit statistics were examined in selecting numbers of classes. ICs follow the principle of parsimony controlling for overfitting and providing a standardized way to balance sensitivity and specificity (54). The following ICs were considered: the Bayesian Information Criterion [BIC; (55)], the Akaike Information Criterion [AIC; (56)], the Constant AIC (CAIC), the Sample Adjusted Bayesian information criterion (SABIC), and the bootstrapped likelihood ratio [BLRT; (57)]. The BLRT test compares the improvement between K-class model with a K-1 class model, providing *p*-values that can be used to justify the inclusion of one more class. Finally, we examined the accuracy with which models classify individuals into their most likely class by considering the entropy of each model. Entropy values range from 0 to 1 and indicate the clarity of class specification, with scores closer to 1 indicating better fit of the data into the prescribed class structure. According to the recommended fit indices (52), the optimal class solution would have the lowest BIC values, lowest AIC values, lowest CAIC values, lowest SABIC values, a significant BLRT *p* value, relatively higher entropy values, and conceptual and interpretive meaning. Furthermore, when comparing a K-class model with a K-1 class model, a significant BLRT test indicates that the model with K classes is optimal.

Furthermore, information criteria were depicted through "elbow plots" showing the improvements related with additional classes (53). More specifically, the optimal number of classes should be the value at which the slope flattens, plus and minus a class.

Then, we analyzed the associations between the identified classes and the sociodemographic variables of the participants. In this sense, the consideration of predictors should not qualitatively change the classes (49). More specifically, we regressed the latent classes on age, age of first use, sex, and employment (yes/no) in a series of multinomial logistic regressions. The R3STEP method in MPlus (58–60) was used.

RESULTS

Participant Characteristics

A cross-sectional survey study was carried out. From the starting 1,354 questionnaires, 265 were removed because of missing responses (> 5%) about relevant variables to this study. The final sample comprised 1,088 subjects.

As shown in **Table 1**, slightly more than half (51%) were female and the mean age was 45.85 (SD ± 10.82) years. Regarding employment, 53.5% were employed. Characteristics of the sample are summarized in **Table 1**.

Latent Class Analysis

Fit indices resulting from the latent profile models containing up to 6 classes are provided in **Table 2**.

Taken as a whole, the 2-, and 3- class solutions showed the better fit as they were supported by the BIC and ABIC values, and BLRT tests (**Table 2**). Then, we compared the 2-, and 3-class solutions. Comparisons of the AIC, BIC, and ABIC values for all the models were contrasted in an elbow plot (**Figure 1**). Nylund et al. (52) suggest that lower BIC, AIC, CAIC and ABIC values indicate a better fit in class selection. However, for both 2- and 3- class solutions those values did not differ greatly across models. In addition, although BLRT distinguishes between class models (52), BLRT significance values did not differ across the two solutions, so we examined both options considering whether classes were theoretically meaningful and interpretable. We inspected the proportion of participants in each class finding that, concerning the 3-class solution, the smallest class drastically dropped to <5%. Although the principle of parsimony is generally to be followed, in our case adding a third class resulted in the addition of a well-defined, qualitatively distinct and theoretically meaningful class. Thus, the interpretability and clinical utility of the 3-class model was superior. This solution provided a reasonable level of classification accuracy, with an

entropy value of 0.861. These results clearly suggest the high level of classification accuracy of these solutions, with average posterior probabilities of class membership varying from 0.69 to 0.96 ($M = 0.85$), with low cross-probabilities, ranging from 0.014–0.189 ($M = 0.072$).

TABLE 1 | Demographic characteristics of the patients according to the type of high-dose.

		n	%	M	SD
Sex	Male	534	49.1%		
	Female	554	50.9%		
Age (years)				45.85	10.82
Employment	yes	582	53.5%		
	no	506	46.5%		
Age of first BZD use (years)				30.60	10.68
Continuous use of BZD (months)				92.97	88.34
Reason for BZD use					
Anxiety	yes	347	31.9%		
	no	741	68.1%		
Panic attacks	yes	77	7.1%		
	no	1,011	92.9%		
Insomnia	yes	617	56.7%		
	no	471	43.3%		
Drug-seeking behavior	yes	137	12.6%		
	no	951	87.4%		
other reasons	yes	96	8.8%		
	no	992	91.2%		
Heroin	no	923	84.8%		
	former	133	12.2%		
	yes	32	2.9%		
Cocaine	no	810	74.4%		
	former	216	19.9%		
	yes	62	5.7%		
THC	no	862	79.2%		
	former	184	16.9%		
	yes	42	3.9%		
ALCOHOL	no	747	68.7%		
	former	193	17.7%		
	yes	148	13.6%		
DDDE (mg)				382	483

BZD, Benzodiazepine; DDDE, diazepam equivalents; M, mean; SD, standard deviation; THC, tetrahydrocannabinol; BZD, benzodiazepines and polydrug misuse.

The retained 3-class solution is represented in **Table 2**. Class 1 represents 4.3% of the sample ($n = 47$, latent class membership probability = 0.69) and participants in this class had the highest probabilities of using cocaine (53%), and alcohol (56%). Thus, this class was labeled as Polysubstance BZD users. Class 2 represents 17.2% of the sample ($n = 186$, latent class membership probability = 0.91) and participants in this class had the highest probabilities of being former heroin (62%), cocaine (77%), THC (66%), and alcohol users (36%). Thus, this class was labeled as Former polysubstance BZD users. Finally, class 3 represents 78.5% of the sample ($n = 855$, latent class membership probability = 0.96) and participants in this class had the highest probabilities of not using heroin (99%), cocaine (94%), THC (95%), and alcohol (77%). Thus, this class was labeled as mono-dependence BZD users.

Table 3 shows the sociodemographic predictors of the LC membership, including sex, age, age of first use, and employment. We performed a series of logistic regression analyses (R3STEP) where the categorical latent class variable was regressed on sex (0 = male; 1 = female), employment (yes/no), and the continuous age variables (**Table 4**). This analysis showed that males were more likely than females to be in class 1 (Polysubstance BZD users; OR = 17.83), and class 2 (Former polysubstance BZD users OR = 7.69) compared to class 3 (BZD users). Younger individuals were more likely to be in class 1 (Polysubstance BZD users; OR = 1.13) and class 2 (Former polysubstance BZD users OR = 1.09) compared to class 3. Finally, employed individuals were less likely to be in class 2 (Former polysubstance BZD users OR = 1.62) compared to class 3 (BZD users). Concerning the age of first use, no statistical differences were found among the three classes.

DISCUSSION

Over the past 40 years, BZD dependence has been on the rise as a public health concern around the world (61). The present study aims to examine patterns of polysubstance use among a sample of Italian adults with BZD dependence.

Given its clinical relevance, we aimed to disentangle the patterns of polysubstance use among a sample of Italian adults that were also misusing BZDs. Our findings revealed three main types of BZD-HD users: of these, the vast majority only abused BZDs (78.5% of the sample), while the other two groups were

TABLE 2 | Fit indices for LCA models with 1–5 classes.

Model	LL	#fp	Scaling	AIC	CAIC	BIC	SABIC	Entropy	BLRT
1 Class	−2884.35	8	1.000	5784.69	5832.63	5824.63	5799.22		Na
2 Classes	−2496.35	17	1.015	5026.70	5128.56	5111.56	5057.57	0.863	< 0.001
3 Classes	−2482.87	26	1.070	5017.74	5173.53	5147.53	5064.95	0.861	< 0.001
4 Classes	−2475.28	35	1.038	5020.57	5230.29	5195.29	5084.12	0.917	ns
5 Classes	−2469.85	44	1.040	5027.70	5291.36	5247.36	5107.60	0.881	ns
6 Classes	−2465.77	53	1.000	5037.54	5355.12	5302.12	5133.78	0.919	ns

AIC, Akaike information criterion; CAIC, Constant AIC; BIC,Bayesian Information Criterion; SABIC, Sample adjusted BIC; BLRT, bootstrap likelihood ratio test; LL, log-likelihood; #fp, number of free parameters.

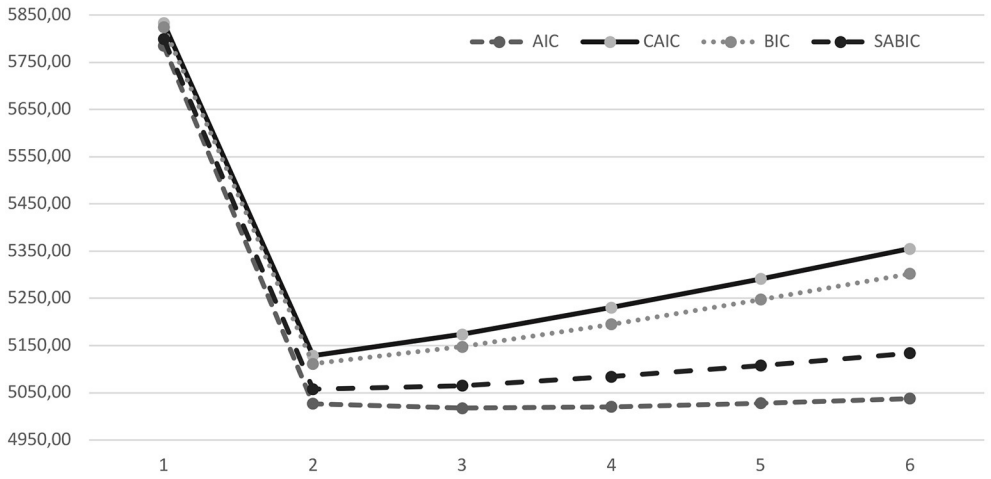

FIGURE 1 | Elbow plot of the information criteria.

TABLE 3 | Characteristics of drugs used and socio-demographics, stratified by latent class.

		Class 1		Class 2		Class 3	
		N	M (SD)	N	M (SD)	N	M (SD)
Sex	Male	38		143		353	
	Female	9		43		502	
Age			38.04 (8.53)		40.46 (7.92)		47.45 (10.92)
Employment	yes	27		80		475	
	no	20		106		380	
Age of first BZD use			25.89 (10.05)		27.85 (9.69)		31.46 (10.76)
DDDE (mg)			416 (432)		412 (474)		373 (488)

BZD, Benzodiazepine; DDDE, diazepam equivalents; M, mean; SD, standard deviation.

TABLE 4 | Odds coefficients for the 3-class model with sex, age, age first use, and employment as covariates.

	Class 1 vs. 2		Class 1 vs. 3		Class 2 vs. 3	
	Estimate (S.E.)	OR	Estimate (S.E.)	OR	Estimate (S.E.)	OR
Sex (Male)	0.84 (1.37)	2.32	2.88 (1.30)*	17.83	−2.04 (0.28)*	7.69
Age	0.03 (0.04)	1.03	−0.12 (0.04)**	1.13	−0.09 (0.01)*	1.09
Age first use	0.26 (0.65)	1.30	−0.08 (0.07)	1.08	0.004 (0.015)	1.00
Employement (Yes)	0.08 (0.75)	1.08	0.22 (0.63)	1.25	0.48 (0.14)*	1.62

*OR, Odd Ratio; S.E., standard error; Class 1, Polysubstance BZD users (n = 47); Class 2, Former polysubstance BZD users (n = 186); Class 3, BZD solo users (n = 855). *p < 0.05, **p < 0.01.*

either more likely polydrug users or former polydrug users. These results highlight that, while the overlap between BZD use and the abuse of other substances is well-documented, a large portion of BZD users are actually less likely to also be using heroin, cocaine and alcohol, as was also reported in other studies (42, 61).

However, the percentage of users who showed a high probability of polyabuse or of being former polyabusers is far from negligible. The simultaneous use of BZDs and other substances is especially concerning given that it may increase the risk of overdose (25), and these two classes of subjects present high treatment complexity.

It is important to note that biological, psychological and social factors influence personal prognoses and treatment responses (62, 63). Many adverse consequences are associated with polydrug abuse, such as an increased fatal and non-fatal overdose (64, 65), self-harm (66), infectious disease (67, 68), risky sexual behavior/risky injection practices (68, 69), criminal involvement (70–72), suicidal ideation/attempt (73, 74), violence and reckless driving (39, 75), mental and physical impairment (75, 76) and social dysfunction (77).

However, the association between these risks and polyabuse (also including BZDs) is not completely clear. Some studies point toward BZD dependence increasing them by markedly increasing disinhibition (73, 74).

Another important aspect is the fact that BZD dependence with greater psychological severity also have poorer treatment outcomes (73, 74, 78).

The most frequent type of patients that we treat in our Addiction Unit is assignable to Class 3, which has the highest probability of not using any substance other than high doses of BZDs. For these patients, treatment with FLU-SI was shown to be efficacious (7).

There seems to be a gender gap concerning the prescription of psychoactive drugs, with BZDs more frequently prescribed to women (79, 80). This study suggests differences in the psychopathology underlying high-dose BZD use: on one hand males tend toward polydrug use, and on the other hand BZD-only users are for the most part female. The latter scenario might be due to several causes, including females being more prone toward anxiety and mood disorders requiring medication, and the tendency to prescribe BZDs more to women (81, 82). Women, in order to soothe psychological distress, tend to call on medical attention more than men, who more frequently resort to other means outside the healthcare system, e.g. alcohol use (83).

The third class is the most numerous among women, also suggesting that BZD addiction could be a cross phenomenon, not only concerning subjects with a history of polyaddictions. This is interesting, because our results suggests that BZD addiction could be a problem that involves a large segment of the general population.

Concerning both age and sex, we found that young men had a higher probability of being included in classes 1 (Poly-substance BZD users) and 2 (Former polysubstance BZD users). Several studies in the general population support the fact that the male sex and a younger age are associated with binge alcohol and cannabis use (33, 84). Women with cocaine and heroin addiction seem less likely than men to develop a comorbidity to alcohol (85). Since the 1980s, studies on heroin and cocaine users have indicated that women present a shorter-lasting addiction than men, and they enter in treatment at a younger age (86, 87). Westermeyer and Boedicker (88), regarding the abuse of multiple substances and their respective treatment, indicated that women progressed more quickly from drug use to dependence: that is, women used each drug (except cocaine) for a shorter period, while rates of dependence remained constant. Moreover, women entering treatment exhibited a more severe clinical profile due to the greater consequences of drug use/abuse in women relative to men (85, 89–91).

The present analysis had several methodological limitations. First, data from the present study are cross-sectional, therefore we cannot make causal conclusions about findings. Second, data were from retrospective, self-report measures. There is the risk that substance use could be underreported when comparing self-report measures with biological markers (92). In fact, despite the self-report measures finding a wide use in the context of substance abuse problems (93, 94), their use is still a matter of debate, due to the limitations related to their use, such as the patients' desire to show a positive self-image or difficulties in remembering consumption episodes and dosages taken (95). Third, information on lifetime or past year use was not available for all substances except BZDs. Fourth, actually there is no a clear definition of high dose of BZD. Finally, we were unable to examine subgroup differences between types of non-medical prescription BZD use.

CONCLUSION

The present study underlines three different classes of BZD high dose abusers. The third class is the most represented and presents a mono-addiction (high dose BZD addiction). Our results and clinical experience highlight the need for a stricter control of BZD use, ranging from prescriptions to sales. While other BZD abuser studies show a female prevalence, our sample was more balanced regarding sex, but this is the first study with this peculiarity. This study also underlines the potential of LCA in improving knowledge of BZD abusers. Since LCA identifies homogeneous subgroups, this division could be used to plan and choose different and specific treatments. Further studies with LCA could be crucial especially in the field of BZD addiction, which would greatly benefit from more detailed studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by 2822CESC. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FL and RC were responsible for the study concept and design. IP, RC, and LZ contributed to the data acquisition. IP assisted with the data analysis and interpretation of findings. LZ, IP, FF, TZ, AB, and AC drafted the manuscript. All authors critically reviewed the content and approved the final version of the manuscript for publication.

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Addiction Psychotherapy: Going Beyond Self-Medication

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Scientific and clinical work concerning the etiology of substance use and addiction has come a long way in the past decades. Current theories highlight the notion that addiction is rooted in deficits in neurobiological and psychological reward mechanisms, but also as a coping-oriented effort to contend with, or "self-medicate," negative emotional experiences. As such, contemporary approaches in the dynamic psychotherapy of addiction highlight the compensatory nature of addiction, encouraging clinicians to detect the mental suffering underlying addiction and promote alternative coping behaviors. In this perspective article, the authors advocate for an integrative approach toward understanding and addressing addiction in psychotherapy, acknowledging its biological, psychological and social aspects. We propose that in addition to the regulatory process of self-medication, in which negative emotions are being suppressed, compulsive substance use may also reflect a substitutive function, in which negative emotions are being 'acted-out' through the use of drugs or alcohol. We suggest an integrative clinical approach which addresses these psychological aspects in a sequential manner and discuss consequent benefits for clinicians and patients working with and through addiction.

Keywords: addiction, substance use, self-medication, psychotherapy, acting out

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INTRODUCTION

Understanding Addiction: The Neuropsychological Revolution

During the past three decades, the understanding of addiction and its etiology has profoundly improved following scientific revelations concerning the neurobiological mechanisms underlying the compulsive nature of substance use, as well as new theoretical conceptualizations of the mental phenomenology and etiology of addiction (1, 2). Early social theories have associated addiction with acquired social norms of delinquency and impaired moral values. However, beginning with the 1990s, emerging evidence has pointed out that addiction is in fact associated with structural and functional brain alterations, including deficits in reward, attention, memory and motivation mechanisms (3) attributed to some extent to genetic predisposition, which is yet unspecified but appears to be shared across SUDs rather than substance-specific (2). Further research demonstrated the reciprocal nature of these neurobiological deficits, suggesting that they serve both as a cause for addiction, in predisposing individuals toward the onset of addiction, and as the effect of addiction, in further altering some neurobiological mechanisms, and even genetics, following intensive and prolonged intoxication (4). This paradigm shift led the way to a bio-ethical transformation in clinicians' view of individuals suffering from addiction. The adoption of a disease model of addiction has been manifested by its inclusion in the European and American medical classification manuals, beginning with DSM-III-R in 1987 and ICD-10 in 1992 (5).

In the field of the humanities, writers such as Eduard Khantzian and Gabor Maté have emphasized the nature of addiction as a psychologically coping-oriented mechanism, in which hurt and traumatized individuals try to cope or "self-medicate" their distress by using psychoactive substances (6, 7). According to these authors, coping-oriented substance use has a paradoxical nature: While the psychoactive effect caused by the drug may at times offer temporary relief from mental pain, in the long run suffering may be augmented by intensive substance use and its physical and psychological consequences, while natural and acquired psychological coping mechanisms are often inhibited. As recently summarized by Koob et al. in an integrative psycho-biological model for addiction, individuals enter the "addiction cycle" through deficient reward-related neural circuits and/or aversive physiological and psychological symptoms which are intensified rather than diminished by prolonged substance intake.

Notably, a substantial proportion of addiction is caused by non-substance induced negative emotions (e.g., depression, trauma), thus entrance to the 'addiction cycle' may occur via positive hedonic experience (positive reinforcement), or pursuit of relief from a withdrawal-related or emotion-related aversive experience (negative reinforcement) (8). The concept of coping-oriented self-medication process underlying the behavioral phenomenon of addiction has allowed for better treatment for individuals suffering from addiction, alongside a continuing effort to decrease the stigma associated with addiction (9). In addition to the biological and psychological roots of addiction, its social and interpersonal origins are often highlighted, with writers such as Bruce Alexander and Johan Harri stressing the social context of addiction, as a disorder of social isolation and disconnection (10, 11).

BEYOND SELF-MEDICATION

The biopsychosocial model is now a consensual etiological model in understanding addiction and more so, an emerging clinical practice implemented in many substance abuse treatment units (2). However, psychotherapists who are not specifically trained in addiction psychotherapy, or those unacquainted with this model, may focus on the self-medicating function of their patients' addiction, while undermining other important aspects of their disorder. For those clinicians, relying predominantly on self-medication in understanding and relating to addiction in psychotherapy may serve as an intuitive and pragmatic clinical framework, yet it may also be limiting due to the following reasons: (1) It often undermines the significance of impaired reward mechanisms to formation and preservation of addiction (2) it offers a somewhat narrow scope for understanding the psychological mechanisms underlying addiction, and (3) it denies clinicians a wide repertoire of interventions which may offer a therapeutic benefit while working with clients suffering from addiction.

Despite these limitations, up to date integrative theoretical frameworks for working with clients who suffer from addiction are scarce. In this paper, we propose an initial outline for an integrative model of addiction psychotherapy, based on "theoretical integration," a concept in which several theoretical frameworks are combined to form a treatment approach (12). The case formulation described below is a composite case, synthesizing disguised information from a myriad of patients (13), which demonstrates this integrative theoretical conceptualization and clinical orientation to addiction in psychotherapy.

Laura, A 42-year-old female patient, single with no children, was referred to an outpatient substance abuse treatment unit by her physician after suffering from symptoms of anxiety and co-occurring misuse of tranquilizers. The patient was a classical musician with a long-standing career as a renowned performer. Her father served as her professional manager, dealing with all formal aspects of her career as well as personal matters, while she was allowed to focus solely on her art. However, she reported feeling highly agitated and anxious prior to and during her performances and reported using prescription tranquilizers in increasing amounts in order to relieve her anxiety.

Neurobiological Deficiency

Beginning with the 1990s, emerging evidence has pointed out that addiction is in fact associated with structural and functional brain alterations, including deficits in reward, attention, memory and motivation mechanisms (3, 4). These neurobiological deficits result in a compulsive search and use of addictive substances, which is continued despite negative consequences which follow. In recent years, continuing effort is made in the field of translational science to bridge the gap between these neurobiological evidence and clinical interventions which could be used by psychotherapists in the field of addiction (2). Due to the rewarding and compensatory effects of addictive substances, patients often present an ambivalent stance toward changing their drug-related habits. Evidence has shown that motivation-focused interventions, which strive to resolve or work-through ambivalence, may be beneficial in leading the way for behavioral change (14). In the field of neuropsychological and cognitive-behavioral therapy (CBT), valuable interventions allow patients to alter their response to drug-related cues, thus promoting reduction in drug intake (15).

Upon Admission, Laura's Predominant Mental State Was That of Preoccupation With the Drugs and Its Rewarding Psychoactive Effects. Acknowledging the Neurobiological Aspects of Her Addiction, Laura and the Therapist Successfully Engaged in Motivation-Oriented Discourse Which Allowed Laura to Enhance Her Inner Motivation for Change, Followed by Behavioral Interventions Aimed at Identifying and Avoiding cue-Induced Triggers, Increasing the use of Adaptive Reward-Related Behaviors and Managing Withdrawal and Craving.

Self-Medication

As recently summarized by Koob et al. (8), aversive physiological and psychological symptoms are intensified rather than diminished by prolonged substance intake, via a physical and mental withdrawal syndrome and negative emotional feedback (termed "hyperkatifeia"). According to the Ego psychology,

addiction is attributed to insufficient psychological power to cope with external environment demands and/or inborn drives. For lack of such resources, emotions are rejected as they are not tolerable to the self, using the psychoactive effect of substance use (16).

During the initial stages of psychotherapy, Laura's misuse of her medication has been efficiently identified as a self-medication for her performance anxiety and narcissistic vulnerability, which have been amplified occasionally by professional setbacks. Following this conceptualization, she acknowledged a more subtle fear which has emerged in recent years of becoming professionally irrelevant, outdated, or overmatched. Reframing her use of addictive substances as "self-medication," or an effort to cope with and manage her fears, allowed Laura to acknowledge the underlying psychological triggers for her substance abuse and address them using cognitive restructuring.

Acting Out

The term "acting out" was first coined by Sigmund Freud, who identified a subtle form of defense/coping-oriented mechanism, in which an inner conflict is manifested through behavior (e.g., substance use) in order to avoid its negative emotional context (17). According to Freud and his successors, in the process of acting out, a conflictual thought (e.g., sexual desire, etc.) is substituted with a more tolerable action (18). However, enacted mental conflicts often remain unresolved and are therefore repeated compulsively. Therefore, acting out should be subject to interpretation and working-through in therapy (17).

As Laura's treatment progressed, she began reporting reoccurring episodes of binge drug use during the weekend. During these episodes, she misused neuro-stimulants, namely by snorting of Methylphenidate (Ritalin^{TM}). Laura then disclosed a history of substance abuse, predominantly misuse of prescription medications: opiates (pain killers), neuro-stimulants and hypnotics (sleeping pills), which were carefully concealed by her father as part of his guardian role, and at times of severe dependence treated discretely in private rehab centers. Processed in therapy, these binge episodes of substance use emerged as acting out of her "passion for life," historically restrained by her parents and now extinguished by her own self-discipline. By using drugs, Laura enabled the expression of the vital parts in her inner life, which were suppressed when sober. In treatment, using Schema-focused interventions enabled Laura to decrease her self-criticism and allow herself to get in touch with the vital parts of her self without using drugs.

Influenced by Melanie Klein's elaboration of Freud's theory, object-relation theory has emphasized psychoactive substances' role in acting out aggressive instincts toward the self and others. According to Klein, inborn aggression which is suppressed or split form the "good self" due to social taboos which forbid explicit aggressive expression, eventually lead to an emotional imbalance. Using aaptive defense mechanisms such as "sublimation" (transforming conflictual emotions into socially acceptable behaviors) or "reaction formation" (converting unconscious emotions into their opposite emotions and/or behaviors) allows individuals to regain emotional balance. However, in cases where such defense mechanisms are unavailable due to insufficient ego resources, individuals may turn to maladaptive defense mechanisms (19). In such cases, the use of psychoactive substances may allow for enactment of the suppressed aggression, either via disinhibition and explicit aggression toward other, or via self-destruction, as in the case of addiction (20). Paradoxically, in both cases substance use does not bring relief or promote equilibrium, but rather preserves a vicious cycle, in which intoxication is the root of, and the "solution" to, all suffering (21).

In Laura's therapy, an interpersonal pattern has also emerged in the patient's binge drug intake. These episodes tended to occur at times when she felt insecure or entrapped in her relationship with her father. At time when she felt he was "abandoning" or overshadowing her in his independent professional ventures, she would act-out her separation anxiety by intensive drug intake, immediately retracting her father to the caregiver position. Inversely, at times when she felt discontent with his over-involvement and over-protectiveness, she would use drugs as enactment of her separation-individuation needs and her aggression toward his exclusive possession of a desirable good. This pattern was repeated in her stance toward the therapist, when binge substance use was at times a way to provoke him to become more engaged and attuned, when he failed to be empathic to her needs. The therapist's careful interventions regarding Laura's substance use, as often representing aggressive or rebellious acts, brought Laura relief from her self-criticism.

DISCUSSION

Integrative Model of Addiction Psychotherapy

Carefully distinguishing between the various aspects of Laura's addiction enabled broadening the scope of mutual understanding of her addiction, while expanding the repertoire of the therapist's interventions, the client's insights and alternative behavioral and emotional responses.

We propose that this initial integrative model does not rely on merely technical eclecticism (12), as it captures and addresses the multidimensional nature of addiction. A previous integrative model of addiction psychotherapy suggested integrating various aspects of treatment in a parallel manner, i.e., using various treatment modules simultaneously according to the patient's needs (22). In contrast, our model includes a sequential integration of the various therapeutic factors, in which every aspect of the biopsychosocial etiology of addiction is addressed in the appropriate time and manner. As seen in Laura's case, initial motivational enhancement allowed for a reduction in her compulsive behavior. In turn, behavioral change uncovered the psychological vulnerability underlying her addiction, leading the way for psychodynamic oriented interventions.

We believe that forming a safe and non-judgmental therapeutic alliance allows patients to enhance their inner motivation for change. Once motivation has been consolidated, behavioral goals, such as reduction in substance intake, can be achieved, gradually attenuating the neurobiological modifications caused by genetic predisposition and repeated substance use. In turn, gradual decline in the neurobiological imbalance allows patients to reflect and address the psychological

and interpersonal conflicts and suffering which were suppressed or transformed by their substance use. Our model distinguishes between self-medication and acting out as two distinct psychological features of addiction. In both cases, clients and therapists should work together to uncover and address the underlying mental content, allowing for an adaptive resolution or remedy which will replace the self-sustaining substance use.

We suggest that the sequential change mechanism may in fact be a circular one, as patients often relapse to excessive substance use and it is necessary to retreat to earlier therapeutic modalities. Furthermore, we believe that biological, psychological and social aspects of addiction can be addressed in various ways; therefore our model is an inclusive one, suggesting that additional methods could be implemented in each of its phases. For example, third-wave cognitive interventions such as Acceptance and Commitment Therapy (ACT) are showing promising results (23) and should be considered legitimate means for addressing psychosocial aspects of addiction. As clinicians, we are bound to sensitively observe the diverse nature of substance use and addiction, distinguishing its manifestation as reward deficiency from its psychological and interpersonal compensatory nature. Carefully observing the various mental functions of substance use and addiction (suppression, transformation, etc.) could broaden our understanding of the psychological mechanisms underlying addiction, its phenomenology and etiology. Hopefully, this will allow for a more effective counseling for individuals who use psychoactive substances.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

DF and DT contributed to conception, design of the study, contributed to manuscript revision, read, and approved the submitted version. DF wrote the first draft of the manuscript. Both authors contributed to the article and approved the submitted version.

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STUDY PROTOCOL
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Alter Game: A Study Protocol on a Virtual "Serious Game" for Relapse Prevention in Patients With Gambling Disorder

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Cognitive behavioral therapy (CBT) is the most successful protocol in gambling disorder (GD) treatment. However, it presents some weaknesses, especially concerning relapse prevention (RP). RP is one of the most important therapeutic steps, aiming at managing cravings and to avoid future relapse increasing perceived self-efficacy. Encouraging results come from the blending of psychotherapy and virtual reality (VR), containing gambling cues. The goal of *Alter Game* (approved by the Ethical Commission, Prot. No. 69346) is verifying the efficacy of an innovative psychological treatment for GD based on the integration of traditional CBT therapy and an immersive VR cue exposure therapy using a serious virtual game, which is a game designed for purposes other than entertainment. RP in virtual cue-exposure therapy allows pathological gamblers to manage the urge to gamble and to avoid relapse by becoming aware of which internal and external triggers are related to craving. We hypothesize that the integrated intervention will be more effective than simple CBT with regard to self-efficacy, craving, and gambling-related distortions. Four virtual ecological environments were developed, and a virtual app, Exludo, interfaced with a computerized multiparametric acquisition system for biofeedback, was created. A sample of about 60 patients aged between 18 and 65 with GD referring to the Addiction Medicine Unit of Verona (Rossi Hospital) will be recruited. Patients will be randomly assigned to the CBT group (16 CBT sessions) or the CBT + VR group (8 CBT sessions + 8 VR cue-exposure therapy sessions). The MCMI-III, the BIS-11, and the SOGS will be used to evaluate inclusion and exclusion criteria, while the *Gambling Related Cognitions Scale* and the *Multidimensional Gambling Self-Efficacy Scale* will be used to verify changes as a function of the treatment. Craving will be evaluated through VAS, and psychophysiological variables will be assessed through biofeedback. A pre-test/post-test experimental design with a 1-month follow-up will be conducted. This study will examine an innovative psychotherapeutic protocol for GD treatment, and it will help in identifying new virtual tools to increase the efficacy of traditional therapeutic approaches that could also be applied to treat other addictions.

Keywords: gambling disorder, virtual cue-exposure therapy, serious game, relapse prevention, craving

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INTRODUCTION

Gambling disorder (GD) is the first behavioral addiction to be approved in the DSM-5 [Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (1)], in which it is included in addictive disorders rather than in impulse-control disorders. Indeed, GD presents more similarities with substance-use disorders than with impulse-control disorders (2, 3), as the persistent and current pattern of gambling associated with GD presents symptoms such as tolerance and withdrawal that are typical of addiction (1). In Europe, GD prevalence rates range between 0.12 and 5.8% (1), but it often goes undiagnosed and untreated, and it is associated with negative health measures (4, 5). GD is one of the *new addictions* that affect people in terms of substantial clinical distress in terms of their social life, work, training, and education (1), as well as from a psychosomatic point of view. Thus, focusing on the efficacy of diagnostic and therapeutic measures for this disorder with a scientific approach is especially relevant to deliver patient-tailored treatments (6). Further studies are needed to compare the efficacy and acceptability of individual and combined psychosocial and pharmacological interventions to deliver patient-tailored treatments.

To address this issue, the current study protocol—*Alter Game-* is aimed at (1) developing an innovative psychological treatment for GD by using a virtual reality (VR) approach, and (2) verifying its efficacy. The rationale for using this approach in GD treatment lies in the fact that cognitive behavioral therapy (CBT) is the most grounded and effective theoretical and applied approach to treating addiction (7). Moreover, a review of evidence-based best practices in GD treatment demonstrated that psychological interventions are the most successful protocols, especially concerning motivational and CBT therapies (6, 8), confirming the findings of the Cochrane review (9). In GD treatment, CBT considers cue exposure therapy (10), cognitive restructuring, problem solving techniques, social skills training, and relapse prevention (11) as fundamental steps. Among them, relapse prevention (RP) is one of the most important steps for GD. Based on the RP model proposed by Marlatt and Gordon (12) for substance abuse, the RP model applied in CBT is focused on a set of cognitive and behavioral strategies to prevent or limit relapse episodes. In general, the RP model refers to immediate determinants (e.g., high-risk situations, coping skills, outcome expectancies, the abstinence violation effect) and covert antecedents (e.g., craving, lifestyle imbalances, and urges) (13). RP therapy aims to find, along with the patients, the factors or situations that can precipitate or contribute to relapse episodes and teaches patients how to manage them, increasing their perceived self-efficacy. Self-efficacy is the degree to which an individual feels confident and capable of performing a certain behavior in a specific situational context (14). The presence of low perceived self-efficacy may contribute to maintaining pathological gambling behavior (15). CBT presents different advantages in pathological gambling treatment; there are lower risks of relapse during the follow-up period, and it has a limited duration and involves structured interventions with long-term positive effects (16, 17). On the other hand, CBT presents some limits. Indeed, difficulties were detected in the treatment of pathological gamblers with high levels of sensation seeking and problematic emotional regulation, in which a higher drop-out rate and higher frequency of relapse emerged (18, 19). Thus, the improvement of CBT efficacy for GD is necessary, especially concerning RP. For this reason, there is a need for innovative methodologies to support traditional intervention techniques.

Encouraging results in this regard have come from the blending of psychotherapy and VR, an immersive computer-generated three-dimensional virtual environment, which is viewed through a head-mounted display (HMD) and interacted with by using controllers (20, 21). VR has been the focus of international interest for the last 20 years or so. Virtual applications are used, in particular, in psychotherapeutic interventions for the treatment of post-traumatic stress disorder (22), social anxiety (23, 24), paranoia (25), specific phobias, such as acrophobia (26), aerophobia (27, 28) and arachnophobia (29, 30). Recent literature has also recently pointed to the usefulness of VR in the treatment of GD (31–34), since VR is a methodological approach that allows to recreate a realistic ecological representation of craving situations (35–37). It has been shown that virtual environments containing gambling cues elicit cravings of the same intensity as those induced by real gaming-related stimuli (e.g., real and virtual slot machines) (31). Craving is defined by the DSM-5 as a persistent, intense or irresistible desire for a specific substance (1) or, in the case of gambling, for an addictive behavior. Craving presents cognitive, emotional, and behavioral characteristics, and it is classified in three different types: reward, relief, and obsessive craving (38); therefore, RP in virtual cue-exposure therapy allows pathological gamblers to manage their urge to gamble and to avoid relapse, given that they become aware of which internal and external triggers are related to craving. The idea of targeting VR for the implementation of RP interventions is supported by other advantages of its application in psychotherapy. Indeed, a patient can experience himself/herself within a protected environment, taking advantage of the possibility of interrupting the virtual experience when he/she feels discomfort or difficulties. The virtual exposure is constantly supervised by the therapist through a monitor: what gamblers see through the HMD is, at the same time, watched by the psychotherapist as well. Furthermore, the ecological validity of the environments guarantees greater generalizability of the skills acquired in VR to daily life environments and situations (39).

However, studies on the use of VR with gamblers present some limits. Some studies were conducted on small samples that, sometimes, did not include pathological gamblers (10, 31, 34). Other important weaknesses that could be improved are the following: (a) distinguishing the physical activation due to gambling craving from the one due to possible cybersickness, i.e., discomfort, apathy, nausea, drowsiness, disorientation, eyestrain, and fatigue that may be elicited by an experience in immersive VR (40, 41); (b) using virtual gambling stimuli in association with other virtual addiction triggers (such as alcohol), (c) using VR with other psychotherapeutic techniques, like mindfulness (31); (d) exploring the role of sense of presence in virtual experiences. Sense of presence is a mental manifestation (42), a cognitive state which is consistent with a subjective feeling of "being there," in

a given virtual environment, which is different from the physical one and whose fruition is mediated by a device (43).

Keeping this background into account, the present *Alter Game* study was designed. *Alter Game* aims at developing an innovative psychological treatment for GD by using VR and verifying the efficacy of an innovative psychological treatment for GD based on the integration of traditional CBT therapy and VR approach. To that goal, we aimed at creating a virtual serious game to prevent relapse in gambling behavior by increasing self-efficacy in managing craving and emotional states and by reducing perceived gambling craving. Indeed, virtual environments are made *ad hoc* for the exposure of patients to specific gambling cues, directed at the detection and management of craving. We chose self-efficacy and craving as dependent variables because they are key aspects in maintaining abstention from gambling. Gamblers that perceive good self-efficacy in managing cravings present a lower probability to relapse, on the basis of the Marlatt RP model (12); thus, craving itself is an important relapse risk factor to be managed and recognized. On the other hand, perceived self-efficacy is a protective factor against relapse (12). Moreover, in response to the above-described limitations in previous studies applying VR approach to gambling treatment, *Alter Game* aims at evaluating the sense of presence through multiple means: the *Independent Television Commission's Sense of Presence Inventory* [ITC-SOPI (44)]; the use of diaphragmatic breathing to manage craving; the presence of cigarette packs, lit cigarettes, snacks, alcoholic beverages (wine, beer), and wine glasses in the specific virtual environments; the use of biofeedback to measure the psychophysiological activation. Cue reactivity, indeed, is measured across several domains of human functioning. The most commonly collected measures are self-reports that assess craving or the desire for a particular substance and physiological responses, which usually include those controlled by the autonomic nervous system, such as heart rate, skin conductance, and skin temperature (45). Psychophysiological arousal is a potential proxy indicator of craving as a reaction to gambling-related stimuli. Conditioned stimuli associated with gambling could simultaneously elicit both subjective craving and psychophysiological arousal (46).

Our hypothesis is that an integrated intervention with VR will be more effective than simple CBT for improving self-efficacy and lowering cravings. Furthermore, in line with CBT, we expect gambling-related cognitive distortions to decrease. This goal is very important because gambling-related cognitive distortions mediate the relationship between depressive symptoms and gambling severity (47) and contribute to the maintenance of maladaptive emotional regulation styles to reinforce and support biased beliefs about gambling outcomes and controllability (48).

METHODS AND ANALYSIS

Alter Game was conceptualized by the Addiction Medicine Unit's interdisciplinary team at the G.B. Rossi Hospital in Verona (Italy). The hospital has signed a collaboration agreement with the Department of Neuroscience, Psychology, Drug, and Child's Health, Section of Psychology in University of Florence (NEUROFARBA—Italy) for methodological and psychometric consultancy related to the study protocol.

Study Protocol Steps

Development and Creation of Virtual Environments

To carry out the study, four virtual ecological environments structured according to the above goals have been developed, created, and tested. We built a cue-free virtual medical psychological office (see **Figure 1**), a city street with access to a tobacco store and a slot room (see **Figure 2**), a tobacco store (see **Figures 3**, **4**), and a slot room (see **Figures 5**–**8**). All of the environments, except for the medical psychological office, have also been structured as empty, i.e., without cues, because cue exposure comprises a series of hierarchical stages that gradually provoke craving (10). We chose these environments on the basis of the most frequently reported gambling activities by gamblers (49) and the activities most commonly associated with higher rates of problematic gambling according to literature (50, 51). The medical psychological office was created to facilitate gamblers in the acquisition of skills to use virtual instrumentation and to manage the relaxation phase present in systematic desensitization during the virtual cue-exposure therapy. Gamblers will interact only with a radio to play a relaxing song. They will not be permitted to gamble in any one environments: it will not be possible to start the slot machine and play scratch cards, for example. More emphasis was placed on game-related sound stimuli that constitute a strong appeal for the patient and, therefore, require a targeted desensitization intervention (52, 53). In the slot room, a non-smoking room was created. In the tobacco store, a clock was inserted and marked the exact, real time.

Virtual environments have been created in photorealistic quality and in a "cybersickness-free" mode in order to offer the patient a virtual experience that would be as comfortable as possible, without any unpleasant effects. Indeed, cybersickness consists in a feeling of malaise due to headaches, nausea, vomiting, or dizziness, and it is triggered by the incompatibility between the inputs reaching the brain through the visual sensory channel and those responding to one's real movement (54). To achieve this goal, patients will be able to move within the virtual environment through "real" steps whose movement would be faithfully reproduced in the virtual environment. Moreover, gamblers may use teleportation if the position to be reached is distant and beyond the play area. Through the joystick, it is possible to point to the place to reach, and the virtual experience will restart exactly from the selected point. VR environments run on this VR hardware requirement: (a) HTC Vive PRO Full Kit with a wireless adapter (see **Figure 9**); (b) PC-Gaming Intel Core i7-9700K—GeForce RTX 2070 8GB-−16GB DDR4-−480GB SSD—Windows 10—Wi-Fi; (c) a 49" or 55" TV monitor.

Software development included the creation of a virtual app, *Exludo*, which was interfaced with a computerized multiparametric acquisition system for biofeedback: EvU-TPS with BIOGRAPH INFINITI and DE-STRESS suite software (see **Figure 10**). This software includes the following features: video recording of the virtual sessions, psychophysiological

FIGURE 1 | Medical Psychological Office.

FIGURE 2 | A city street with access to a tobacco store and a slot room.

FIGURE 3 | A tobacco store.

FIGURE 4 | A tobacco store with a view of the slot room.

FIGURE 5 | A slot room.

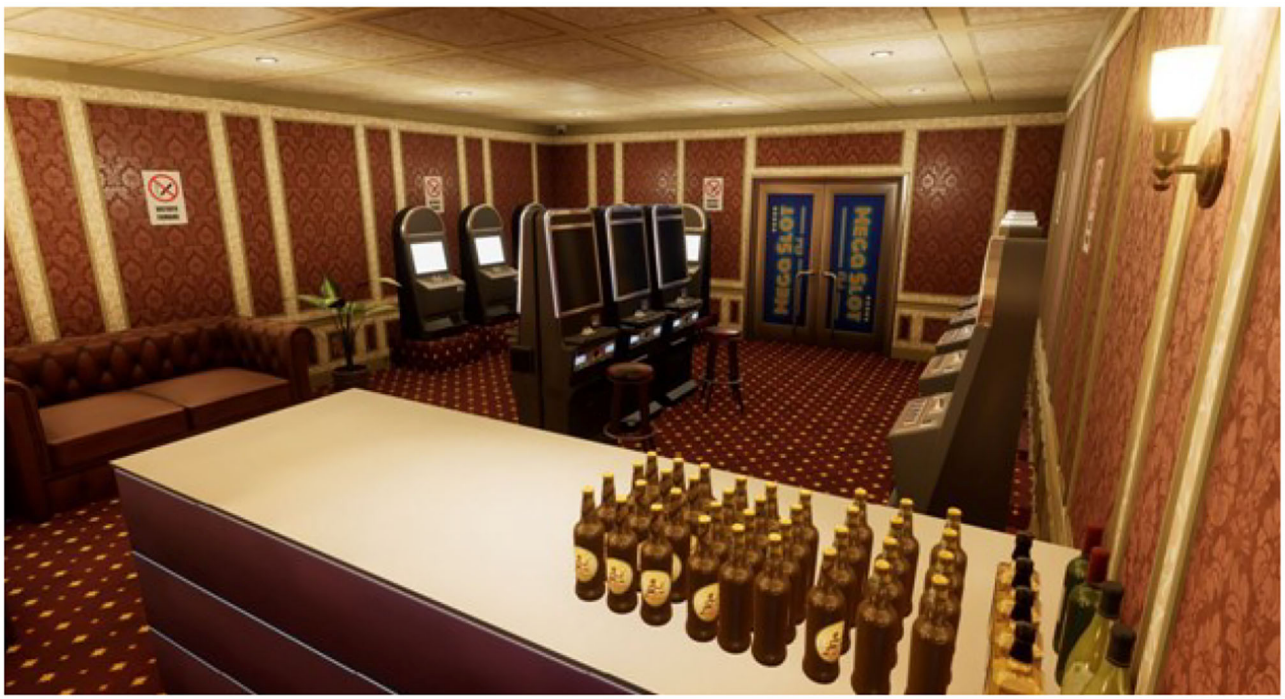

FIGURE 6 | A slot room with some alcohol cues present in Exludo.

parameter recording, and the integration of software that allows the therapist to configure the settings of the experience by operating in first person in the VR with a Drag'n'Drop interaction system. Drag and drop indicates a succession of

FIGURE 7 | The non-smoking slot room with some slots turned off and on.

three actions, consisting of clicking on a virtual object to drag it to another location within the virtual environment, where it is released. Virtual environments will remain the same for all patients and for the entire duration of the study. A wireless, cable-free kit was chosen for both the virtual hardware and biofeedback instrumentation for the patients' safety. Given the COVID-19 pandemic, appropriate accessories were also employed: disposable, non-woven, breathable face masks for HTC Vive PRO, waterproof and hygienic replaceable feather rubber for HTC Vive, and hygiene devices (spray, hand sanitizer gel, surgical masks) were used to guarantee the hygiene of the instruments and the patients' safety.

The design and implementation of the virtual environments that were created *ad hoc* for this study required a development period of about 6 months, in an interdisciplinary mode. Close collaboration between psychologists, programmers, and the 3D developers of Plumake S.r.l., who provided both the hardware and the *Exludo* software, was necessary. All of the environments were created *ex novo* and starting from real cues related to gambling (scratch cards, slot rooms, SuperEnalotto, snacks, cigarettes, etc.). The trade names of each of the 3D objects that were reproduced were changed due to the presence of the respective copyrights. After the creation of *Exludo*, a testing phase of the virtual hardware and software was planned and concluded in about 2 months. This phase was important in order to provide for the replacement of non-functional equipment and the correction of any bugs, i.e., errors in the writing of the software, which could interrupt the virtual experience or distort some of the environments' features. During the testing phase, a psychologist noticed some bugs in the movement system and in the interface between the biofeedback software and *Exludo*. Each environment was repeatedly tested to find as many errors as possible. The software has also been optimized in terms of usability, especially concerning the main start-up interface and the menu for selecting the actions to be taken. These changes guarantee an intuitive and immediate use of the application. A user guide was created by a psychologist and a programmer for the installation and the use of the hardware and software. A 10-h service package has been provided with respect to the hardware and software packages. Moreover, the correct functioning of the EvU-TPS biofeedback software had already been tested by the Medical Engineering Service of the

FIGURE 8 | A red wine bottle, a wineglass and a lit cigarette in the slot room.

Integrated University Hospital of Verona, and its interfacing with the virtual application was verified to ensure a reliable measurement of the parameters focused on the aims of *Alter Game* with respect to the detection of physiological activation due to craving. Righetto S.r.l. took care of the transport and assembly of the biofeedback instrumentation.

Measures

The second step of *Alter Game* was focused on the definition of the measures and procedure involved in the study.

Self-Report Instruments for the Assessment of Inclusion and Exclusion Criteria in the Intervention

Patients with GD between 18- and 65-years being part of the first and the second pathways of gamblers based upon Blaszczynski and Nower's classification (55) will be enrolled. They will comprise both" behaviorally conditioned problem gamblers" and" emotionally vulnerable problem gamblers." The third pathway, comprising" antisocial impulsivist problem gamblers," was excluded because these gamblers present high levels of impulsivity, and then they might be much more exposed to relapse after VR exposure than the other pathways.

The *Millon Clinical Multiaxial Inventory—III* [MCMI-III (56, 57)], the *Barratt Impulsiveness Rating Scale* [BIS-11 (58); Italian version (59)] and the *South Oaks Gambling Screen* [SOGS (60); Italian version (61)] will be used to evaluate the inclusion and exclusion criteria. The MCMI-III is a clinically oriented instrument, which is used in the assessment of personality disorders. The test comprises 175 dichotomous true/false items, 24 scales, and 4 correction indices. The questions investigate the presence of borderline and antisocial personality traits, thought disorders, and delusional disorders. The MCMI-III showed excellent construct validity, test-retest reliability, as well as internal consistency even if translated into several languages (62). Its factor structure is consistent across countries (63). The cut-off scores considered as exclusion criteria are: scores $\geq$ 75 on the "6A- Antisocial" scales in the "personality styles" section, "C-Borderline" in the "severe pathology" section, "SS-thinking disorders" and "PP-delusional disorders" in the "severe syndromes" section. Protocol invalidating scores: V scale: 2-3 points; X scale: $\leq$ 34 or $\geq$178.

The BIS-11 is a 30-item self-report scale, validated in Italian, which assesses impulsiveness. All items are rated on a 4-point scale, where 1 stands for rarely/never, and 4 stands for almost always/always. The BIS-11 proved to be a reliable psychometric instrument for measuring impulsiveness (59). The cut-off score considered as an exclusion criterion is $>$ 65.46 + 12.08 (SD) (64).

The SOGS is a questionnaire that comprises 16 items that assess the presence of pathological gambling behavior. Good validity of the instrument has been demonstrated, particularly in terms of sensitivity and specificity (60), also in the Italian population (65). SOGS detects the type of gambling games played by gamblers. The cut-off score considered as an exclusion criterion is $\leq$ 4.

FIGURE 9 | HTC Vive PRO.

Pre and Post-test Follow-Up Measures

The *Gambling Related Cognitions Scale* [GRCS (66); Italian version (67)] and the *Multidimensional Gambling Self-Efficacy Scale* [MGSES (68)] will be used for the evaluation of changes in the experimental variables as a function of the treatment.

The GRCS is a 23-item scale that detects cognitive distortions on the basis of five specific erroneous thoughts: gambling expectations, illusion of control of fate, predictive control of an outcome, inability to stop gambling, and interpretative distortions. The patient responds to each item on a 7-point scale, ranging from 1 (completely disagree) to 7 (completely agree). Expectations related to gambling and the effects of gambling are an expression of the level of salience of the gambling experience and the effect expected from the activity of gambling. The illusion of control of fate is the belief that one can influence the outcome of the bet through the study and application of certain gambling strategies or by means of (magical) tools, such as lucky charms. Predictive control of the outcome is the prediction of the outcome of bets on the basis of feelings, perceptions of environmental traces that suggest the presence of positive or negative influences, or on the basis of pseudo-statistical reasoning on the probability of winning. The inability to stop gambling, i.e., the subjective feeling and belief of not being able to control the game is a dimension that expresses perceived self-efficacy. Interpretive distortions are thoughts that justify losses and encourage a person to return to gambling. The scale is characterized by good psychometric properties in terms of dimensionality, reliability, and validity both in its original version (66) and in the Italian adaptation (67).

The MGSES is a scale that was validated on the Italian population and comprises two sections: the first with 6 items and the second with 11 items, to be rated on a scale from 1 (not at all capable) to 5 (fully capable). The scale measures the gambler's perceived self-efficacy with respect to the management of gambling behavior and self-regulation during stressful situations, negative emotional states, free time, and other factors. The instrument showed good psychometric properties in terms of dimensionality, reliability, and validity in the Italian population (68).

Multidimensional Craving Measurement and Sense of Presence in VR

During VR therapy, craving and the sense of presence in VR training will be measured. Craving will be detected through both subjective and objective measures: a visual analog scale (VAS) to evaluate the perceived craving intensity on a scale from 0 to 10, based on the specific moment in which it will be administered. Furthermore, craving will be objectively evaluated with biofeedback EvU-TPS through the detection of the following psychophysiological measures: heart rate, heart rate variability, skin conductance, and skin temperature. The sense of presence will be measured through the ITC-SOPI self-report at

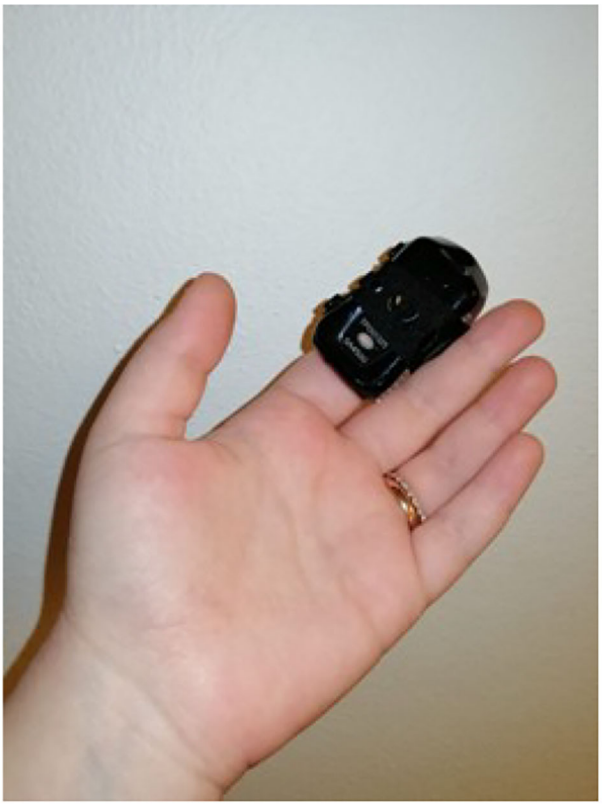

FIGURE 10 | Evu Tps—biofeedback.

the end of the virtual session. The Addiction Medicine Unit in collaboration with NEUROFARBA is working on a study to assess the psychometric properties of ITC-SOPI in its Italian version.

Training Course for Treatment Providers

After the development of the VR environments and the definition of the measures and procedures involved in the study, the next step consisted in training the treatment providers involved (psychologists and psychotherapists) and in a verification of learning after the training course. This represented a very important point as one of the factors that affect the efficacy of interventions in the health domain is the good quality of the training administered to the people who implement the programs (69). Indeed, training allows those who carry out the intervention to become confident with it (70). Moreover, some interventions need certain competencies that can be acquired only with specific training courses (71). In particular, a well-planned training course provides basic theoretical knowledge, clear program goals and objectives, modeling, and practice of effective intervention strategies, regular coaching, and constructive feedback (72). The training course consisted in 2 lessons on biofeedback, 2 lessons on CBT and diaphragmatic breathing, 1 lesson on VR theory, hardware and software application, and hygiene rules for virtual instruments. All lessons lasted 3 h, for a total duration of 15 h of training. Due to COVID-19 restrictions, the lessons were organized in a mixed modality, online and offline simultaneously. Two *ad hoc* questionnaires were created to assess the following variables: the first questionnaire had 13 questions and assessed electrodermal activity, skin conductance, photoplethysmography, heart rate, heart rate variability, the psychophysiological state of relaxation of the participants, their respiratory rate, and biofeedback training. The second questionnaire had ten questions and assessed respiratory training, mastery strategy, disputing, systematic desensitization, VR therapy, and cybersickness.

To analyze the efficacy of the training course for the psychotherapists involved in *Alter Game*, we proceeded to a pre-post design with a follow-up in which the above-listed variables were measured before the beginning of the training course (pre-test), after the last meeting of the training course (post-test), and 1 month after the conclusion of the course (follow-up). The treatment providers were provided with training material in the form of slides and guides to facilitate study and consultation in case of need. The coordinating psychologist sent the questionnaires *via* e-mail the day before the lessons for the pre-test, and then again after the end of each of the expected 2 training cycles. The first cycle included the 2 biofeedback lessons and, the second, the 3 lessons about CBT, diaphragmatic breathing, and VR. All training sessions were organized on the Meet platform, ensuring the mixed modality and the possibility to follow lessons in a deferred mode since everything was videotaped and made available to all the trainees on a shared drive folder. Training was provided by Righetto S.r.l. (as far as electromedical equipment was concerned) and by Plumake S.r.l. (for what concerned the hardware and virtual software dimension), respectively. The meetings concerning the training in psychotherapy techniques and VR therapy were organized by psychologist-psychotherapist collaborators.

Efficacy Evaluation of the Integrated Intervention

Design

We will conduct a pre-test/post-test experimental design with a 1-month follow-up.

Two independent groups to which patients will be randomly assigned will be considered. One group will undergo a traditional CBT treatment of 16 sessions (the CBT group), while the second group will undergo the integrated treatment, consisting of 8 CBT sessions and 8 sessions of psychotherapy based on VR cue-exposure therapy, each with a different environment (the CBT + VR group). Each session will last 1 h. To better control the effects of the training in VR on pathological gamblers, the psychophysiological parameters of craving will be measured through biofeedback and VAS at each session of the training (multi-method measurement of craving).

To verify the efficacy of the intervention, one measurement session is planned before the beginning of the treatment (pre-test), and one at the end of the treatment (post-test). For the assessment of the maintenance of any changes at post-test, an additional measurement is planned 1 month after the end of the treatment (follow-up). The three measurement sessions are planned for both the CBT group and the CBT

+ VR group. In each measurement session, perceived self-efficacy in managing gambling behavior, craving, gambling-related cognitive distortions, impulsivity, personality traits, and pathological gambling symptoms will be measured in both groups.

Recruitment

We will recruit a sample of about 60 patients with GD who are referred to the Addiction Medicine Unit of Verona (G. B. Rossi Hospital). This sample size is consistent with the power analysis we conducted *a priori*. Using G*Power software to estimate the sample size that would be necessary to achieve a statistical power of 0.95 for a mixed ANOVA, indeed, revealed that a sample size of $n = 58$ was necessary in order to obtain an average effect size, equal to 0.40 ($\alpha = 0.05$).

Inclusion criteria will be: (a) being male and female subjects over 18 years of age and under 65 years of age; (b) being addicted to slot machines, scratch cards, lotto, SuperEnalotto (because environments were created with these specific cues); (c) informed consent signature. An inclusion criterion (b) will be evaluated by a clinical interview based on the DSM-5 diagnostic criteria in the first psychological assessment session and by SOGS, which reports the type of gambling games played by gamblers.

Exclusion criteria will be the presence of: (a) antisocial personality traits; (b) borderline personality traits; (c) high levels of impulsivity; (d) thought disorders; (e) delusional disorders. Exclusion criteria (a), (b), and (c) were chosen to identify the presence of gamblers probably categorized as "third pathway" to Blaszczynski and Nower (55) and that, therefore, may be more exposed to risks of relapse following immersive VR exposure to environments with trigger cues. Excluding these patients will allow us to guarantee greater safety for them by administering treatment as usual.

We also identified particularly vulnerable populations that may not be included in the study: (a) patients suffering from epilepsy because HMD can provoke epileptic seizures like other devices that produce visual effects (as described in the HTC-VIVE official user's guide); (b) visually impaired patients and hearing impaired patients because they would have limitations in the use of the virtual experience concerning sounds and visual aspects; (c) patients with cardiovascular problems because our psychophysiological measures of interest could be altered by these pathologies; (d) gamblers with vestibular problems because they may fall during the virtual reality experience due to vertigo, motion sickness, and imbalance (73); (e) patients with neurological disorders: e.g., individuals with migraine are more susceptible to visual discomfort (74); (f) patients with schizophrenia or psychotic traits because the available data on immersive VR in schizophrenic subjects are currently limited (75), and no data were available on gamblers with psychotic diseases and immersive VR treatment.

Patients with the onset of cybersickness for two consecutive virtual sessions will exit from the study *in itinere* and will be able to undertake a path of psychotherapy as usual in the Addiction Medicine Unit.

Interventional Methods

Intervention

Patients will be recruited when they access the Addiction Medicine specialist service "Colma il Gap" for GD at the G. B. Rossi Hospital in Verona, Italy. The selection of the sample will be based on the inclusion criteria. The selection of the patients who may be involved in the study will attend the following procedures. At the first access to the service, the patient will sign the informed consent and will be interviewed for the collection of anamnestic, life/family history, and clinical and gambling history details. We will assess legal and illegal substance use and the presence of addiction during the first psychological examination through a structured interview. It is important to capture sub-clinical factors related to the use of substances that could influence response to VR as well as situations linked with relapse. At the second visit, the questionnaires will be administered to the patient, in a self-completion mode, in the following order: MCMI-III, BIS-11, SOGS, GRCS, and MGSES. If the expected inclusion criteria will not be met, the patient will be excluded from the study but will be taken care of according to the usual treatment.

Patients meeting the inclusion criteria will be randomly assigned to the CBT group or to the CBT + VR group. The CBT group will follow a full cycle of psychotherapy that will consist of 16 weekly sessions, lasting 60 min and will make use of techniques belonging to an evidence-based cognitive-behavioral approach. For the CBT + VR group, there will be a first cycle of traditional psychotherapy that will consist of 8 weekly sessions, each lasting 60 min, which will also make use of evidence-based cognitive-behavioral approach techniques. Following this, psychotherapy based on virtual exposure will be carried out, which will again comprise 8 weekly sessions, marked by: systematic desensitization therapy in virtual reality exposure therapy, cognitive restructuring, and emotional management/literacy. Each virtual session will last 60 min, 20 min of which will be dedicated to virtual exposure. About 20 mins is the recommended limit of the duration of immersions in virtual reality because eyestrain and headache may occur for longer exposures (76, 77). We adopted this safety limit at least until empirical data document the safety of VR immersion with gamblers (10). An extinction process needs more time to originate, but limiting the duration of the immersion is necessary due to ethical considerations (10).

The virtual session will be structured as follows. In the first session, the virtual protocol will be presented to the patient, and virtual training will be carried out to provide the skills related to the use of the instrumentation (**Figure 11**). Biofeedback parameters will also be measured 5 min before the session. From the second to the eighth sessions, the biofeedback parameters will be measured 5 min before the beginning of the session (in the study, the baseline rate), and the measurements will be resumed during the entire exposure to the virtual environment. The patient will be asked about the intensity of the craving felt during both measurements and at the end of each session *via* VAS. As mentioned above, the technique used in conjunction with virtual cue exposure therapy will be systematic desensitization, which is a psychotherapeutic CBT treatment consisting in alternating

FIGURE 11 | An example of a subject wearing the virtual reality and biofeedback equipment.

phases of exposure to the trigger cues to phases of bodily relaxation, with the aim of reinforcing the relaxation response even in the presence of specific reactive cues (78, 79).

The systematic desensitization intervention will be structured as follows: the patient will learn a body relaxation technique [diaphragmatic breathing (80)]; the psychotherapist will proceed with the exposure of the patient to the trigger environments in the following order: a psychologist's office, a street with no game-related stimuli, a street with trigger stimuli, an empty tobacco shop, a full tobacco shop with sound stimuli, an empty slot room, a slot room with no audio-video stimuli, a slot room with active slot machines (audio-video stimuli), a slot room with active slot machines and alcohol and tobacco cues. During the virtual exposure to the trigger stimuli, when the patient signals that he/she is feeling a greater psychophysiological activation, the relaxation phase will begin, proceeding according to the following procedure: the patient will be teleported by the therapist to the psychologist's office (cue-free environment), where he/she will activate the radio to start the relaxing music and perform diaphragmatic breathing until psychophysical relaxation is achieved. When the patient is ready for the next exposure to the same trigger stimulus, the therapist will teleport him/her into the previous virtual trigger environment. The therapist will proceed in this way until the end of the time available for the virtual exposure. During the virtual exposure therapy, the psychotherapist will ask the patient to focus on bodily sensations and emerging thoughts and emotions related to gambling craving; after the 20 min of virtual exposure, the topics emerged will be the subject of psychotherapeutic work in the second part of the psychological interview. For both groups, the administration of the scales and questionnaires is scheduled for the nineteenth session; the results of which will be returned in the twentieth session. In the twenty-first session, the follow-up measurements will be carried out 1 month after the end of treatment to also verify the presence of any relapses. In detail, all the steps envisaged by *Alter Game* study are reported with the relative timing in the flow chart below (see **Table 1**); a total duration of about 18 months is expected (see **Table 1**).

Safety and Hygiene Measures

To ensure patient safety and hygiene in the virtual setting, the recommendations of the Italian Higher Institute of Health (HIH) and the following procedures will be followed: (a) Hand cleaning: all subjects trained to handle VR devices shall have an alcohol-based hand sanitizer. Before a user turns on a device, he/she shall wash his/her hands for at least 40 s and following a precise sequence as illustrated on the Ministry of Health website; furthermore, he/she shall use a hydroalcoholic gel, rubbing his/her hands for 20 s (as described by HIH). (b) Ensuring that waterproof foam replacements are fitted to the HMD as the foam present by default does not allow for thorough hygiene. (c) Inserting disposable waterproof masks on HMD before using the viewer and replacing them between patients/treatment providers. (d) Disinfecting joysticks and all objects with which the patients and treatment providers may come into contact in between patients/treatment providers. (e) Sanitizing the EvU-TPS (biofeedback) instrumentation after each use. (f) Patients and treatment providers will be required to wear a surgical mask, respecting the indications of the HIH on the matter. (g) Ensuring that the patient has thoroughly cleaned his/her hands, both with soap and with sanitizing gel before entering the outpatient clinic; in fact, it will not be possible to make him/her wear gloves because of the need to measure psychophysiological parameters by photoplethysmography. (h) Repeating all hygiene procedures in between patients/treatment providers and at the end of each daily session so that the equipment remains sanitized at all times. (i) The hygiene of the surgery and the hospital environment will be guaranteed by the company staff dedicated to this purpose. (l) To sterilize the virtual reality devices, the product TRISEPT COMPLEX will be used, which is available at the warehouses of the internal pharmacy of the G.B. Rossi Hospital of Verona, Italy.

TABLE 1 | Flowchart of Alter Game study.

Alter game steps	Timeline							
	Week 0	Week 1	Week 2	8 weeks	8 weeks	Week 19	Week 20	Week 25
Design and implementation of virtual environments								
Hardware and software installation and testing								
Training course for Treatment Providers								
First phone contact with patient								
Patient informed consent obtaining								
Data collection about the patient demographic characteristics, medical history and clinical history concerning GD								
Pre-test (MCMI-III, BIS-11, SOGS, GRCS, MGSES)								
Restitution of pre-test results to the patient								
Inclusion/exclusion criteria + randomization into CBT group and CBT + VR group								
First psychotherapy cycle (8 sessions of traditional psychotherapy for both groups)								
Second psychotherapy cycle (8 sessions of traditional psychotherapy for CBT group and 8 sessions of psychotherapy based on virtual reality for CBT + VR group)								
Post-test (MCMI-III, BIS-11, SOGS, GRCS, MGSES)								
Restitution of post-test results to the patient								
1-month follow-up (MCMI-III, BIS-11, SOGS, GRCS, MGSES)								

GD, gambling disorder; MCMI-III, Millon Clinical Multiaxial Inventory-III; BIS-11, Barratt Impulsiveness Inventory-11; SOGS, South Oaks Gambling Screen; GRCR, Gambling Related Cognitions Scale; MGSES, Multidimensional Gambling Self-Efficacy Scale; CBT, cognitive behavioral therapy; VR, virtual reality.

(m) The use of an ultraviolet (UV) light box that sterilizes all virtual instrumentation without the use of chemicals that could damage the devices will be considered. Indeed, UV light can damage or destroy various types of viruses such as SARS and MERS (81). At the moment, some companies are working on some prototypes.

DATA ANALYSIS

In general, all the patients' demographic and clinical characteristics will be summarized using descriptive statistical methods. In particular, mean, median, and standard deviations will be used for symmetrically distributed continuous variables, median and interquartile distance for asymmetrically distributed continuous variables, and frequency distributions for categorical variables. Multi-method analysis of craving measurement in order to draw up a physiological and psychometric profile of craving (using biofeedback) will be performed. This analysis will be conducted through linear correlation measures. For the analysis of the efficacy of the training course for the treatment providers, Student's *t*-tests for dependent samples or Wilcoxon's non-parametric test for paired samples will be used. Contingency tables and McNemar tests may also be used. For the analysis of the efficacy of the CBT + VR group compared to the CBT group, a mixed ANOVA will be performed for repeated measures with *Time* as within factor (pre-test/post-test/follow-up) and *Group* as between factor (the CBT + VR group/the CBT group).

Moreover, we will pay attention to the issue of an attrition rate. We are expecting to find a retention rate of at least 80% (78, 79) to avoid that participant loss will bias research outcomes. After that, we will check for any significant difference between the two treatment groups (CBT and CBT + VR) to verify if there is a differential attrition rate. In particular, we will compare the average number of meetings attended by the participants between the two treatment groups through *t*-tests, and we will compare the presence of drop-outs across the two groups through Chi-square tests. Moreover, we will determine if there are any significant differences (at the baseline) between participants who will complete the post-test session and those who will not in order to verify if specific subgroups of participants have a higher drop-out risk. This analysis will be conducted separately for each group. If any significant differences between participants of the two treatment groups will be found, we will verify that systematic attrition does not occur and we will conduct the analyses to verify the effects of the two interventions (CBT and CBT + VR) with the participants who completed the baseline and post-test assessments. Those lost to post tests will be excluded. If significant differences between participants of the two treatment groups will be found for the average number of meetings attended and the treatment drop-out, and participants who will complete the post-test session will be significantly different from those who will not, subsequent analyses will be conducted by using the last observation carried forward (LOCF) to assess the effects of attrition. Furthermore, we will examine within-group changes in outcomes as a function of session attendance to assess the effects of intervention non-compliance on outcomes. These subsequent analyses will be conducted, not excluding participants who will be lost to post-test and by imputing values for the follow-up variables for the participants who will not complete the post-test assessment.

DISCUSSION

A recent review has confirmed the efficacy of CBT to treat various addiction problems (7) and, especially, GD (9). Several published clinical studies have used VR to treat different psychopathological problems (anxiety, PTSD, depression, etc.), with a lot of them underlining that CBT and VR combined could improve the efficacy of social anxiety disorder and paranoia treatments (22, 24). Indeed, VR is a methodological approach that allows to recreate a realistic ecological representation of craving-eliciting situations (34–36). However, as of yet, no clinical study of CBT and VR in GD treatment has been conducted. Keeping this background into account, the necessity to develop a new study protocol—*Alter Game*– emerged. In detail, *Alter Game* aims at developing an innovative psychological treatment for GD by using VR and verifying the efficacy of an innovative psychological treatment for GD based on the integration of traditional CBT, coupled with a novel VR approach.

Based on previous studies, suggesting that CBT and VR combined are more efficient than CBT or VR only (23, 25), we aim at confirming this evidence in gambling addiction by taking specific target variables into account, such as self-efficacy, craving, and cognitive distortions. We can hypothesize that CBT and VR combined will be more effective than CBT only. In particular, at the conclusion of the psychotherapy sessions, we expect to find a higher increase of self-efficacy and a greater reduction of cravings and cognitive distortions—in terms of effect size—in the case of the integration of CBT and VR. To better evaluate these expected results, we aim at using biofeedback in order to observe and measure the psychophysiological activation associated with cue exposure, which would allow us to overcome the limits of self-report craving questionnaires or craving Likert scales. Moreover, we already implemented a training course for the treatment providers to guarantee a correct administration of the psychotherapy protocol with the patients before the study will start.

By increasing self-efficacy and reducing gambling-related craving and cognitive distortions, we aim at reducing the risk for relapse, which represents one of the most important psychotherapeutic steps for GD. Using VR cue-exposure therapy, pathological gamblers may increase their skills to prevent a relapse, or they could improve the management of their gambling craving and identify the triggers associated with it by pinpointing its cognitive, emotional, and bodily characteristics. These skills are important to prevent relapses in gambling behavior and to increase the self-efficacy of gamblers. By decreasing gambling-related distortions, which contribute to maintaining a maladaptive emotional regulation and reinforcing the irrational beliefs about gambling outcomes and controllability (48), we aim at promoting higher levels of management regarding thoughts about gambling in general. Another important aspect to be considered is that VR will provide contexts that are typical of everyday life, contributing to the generalizability of the craving management. Several studies using VR and cue reactivity to evaluate craving and other relapse risk factors in addictions (alcohol, tobacco, drugs, etc.) underlined the influence of life context in maintaining dependence or relapsing (82–84).

Despite these strengths, some limitations must be underlined. As a limitation of the study protocol, the use of self-report measures may be affected by the lack of insight/awareness, inability to identify or articulate beliefs/thoughts, and intentional dissimulation in pathological gamblers. However, the use of self-report measures is inevitable, so we chose tests that present good psychometrics properties, and we will consider the MCMI-III validity scales to control the social desirability index and the assessment protocol validity. In order to better control these biases, future studies could consider the introduction of behavioral tasks that in the Alter Game study protocol are not included except in the therapeutic intervention section. Also, the absence of a control group (non-treatment), which could serve to better analyze the efficacy of the integrated intervention, could be a further point to be addressed in the future. A public clinical service cannot omit to offer clinical treatment to a patient with GD for ethical reasons. Moreover, there may be potential threats to the internal validity of the research design due to its longitudinality, with a possible consequent loss of patients. In line with this, we chose a 1-month follow-up to keep the patients as engaged with the study as possible, since the dropout rate in pathological gamblers is high (18, 19). We are aware, however, that this time may not permit the detection of spontaneous recovery. Furthermore, studies could implement a strategy to better control susceptibility to conditioning. Another important consideration deals with the changes due to the COVID-19 pandemic. Indeed, GD is changing: a lot of patients are addicted to online gambling, so some patients that request our treatment may not respond to our inclusion criteria, in particular regarding the type of gambling activities considered in the *Alter Game* study before the beginning of the pandemic. In the future, the development and creation of new virtual environments on online gambling may be needed. The COVID-19 pandemic also brings additional complications: wearing the surgical mask can cause fogging problems to the HMD that compromise the correct use and the ideal fruition of the immersive virtual experience. In addition, the presence of restrictions for the containment of COVID-19 (lockdown, isolation, quarantines) may hamper the possibility of maintaining the 1 session per week that would be required by the study protocol. Another limitation regards the generalizability of the integrated protocol due to the possible presence of cybersickness and specific medical problems. Indeed, patients that present cybersickness during the virtual treatment or clinical problems like epilepsy, visual or hearing impairments, vestibular or cardiovascular or neurological diseases, and schizophrenia or psychotic traits will not be granted access to CBT + VR psychotherapy. Finally, future developments could improve our virtual environments through the insertion of avatars that interact with gamblers, thanks to artificial intelligence. This will be more expensive, but it may be useful to work on the impact of social interaction in the maintenance of GD and to manage situations in which gamblers are invited to eat snacks and drink alcoholic beverages. Indeed, it is known that social isolation and a sense of loneliness are related to problematic gambling (85, 86). Therefore, inserting

social interaction in virtual gambling-related environments could be an important development to treat these daily experiences that may be relapse risk factors. Subjects that are socially excluded tend to self-medicate their unpleasant emotional states [e.g., anger, sadness, and anxiety; (87)] through emotion regulation processes (88) that can incorporate gambling too (89). Moreover, some studies highlighted that there is an association between gambling and alcohol use: those who drink alcohol more frequently are more inclined to gamble and to experience negative consequences due to their gambling behavior (90–93), as well as increased speed and duration of the game session (94, 95), increased risky wagering (94, 96, 97), and more rapid depletion of available funds (94–96).

To conclude, if our expected results will be confirmed, *Alter Game* could promote new possible tools for RP therapy that may be applicable within specialist-care services for GD and within therapeutic communities. These may also be suitable for poly-addicted gamblers, given the known high comorbidity between gambling and substance use disorders (98). Indeed, if the integrated virtual therapeutic protocol proposed by *Alter Game* will be effective, it could be extended to the treatment of other addiction disorders, reinforcing the traditional RP program.

ETHICS STATEMENT

Approval for the research was obtained from the Ethics Committee for Clinical Trials (CESC) of the Provinces of Verona and Rovigo based at the Integrated University Hospital of Verona, Italy (approval code: 3004CESC with Protocol No. 69346 of 21/12/2020). The latest revision of the Declaration of Helsinki as well as the Oviedo Declaration is the basis for the ethical conduct of the study. The study protocol is designed and will be conducted to ensure adherence to the principles and procedures of Good Clinical Practice and to comply with Italian law, as described in the following documents and accepted, by signature, by the study investigators: ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community. D. L.vo n. 211 of June 24, 2003. D. L.vo n. 200, November 6 2007. Ministerial Decree of December 21, 2007. AIFA Determination, March 20, 2008. All essential clinical records will be retained to demonstrate the validity of the study and the integrity of the data collected. The promoter of this study, in accordance with the responsibilities required by the rules of good clinical practice (Legislative Decree 211/2003) and in accordance with the laws and regulations regarding data protection (including the European Regulation on the protection of personal data 2016/679), will process the personal data that will be collected exclusively for the implementation of the study and for the purpose of device surveillance.

AUTHOR CONTRIBUTIONS

FL and RG: conceptualization. RG: data curation and investigation. MD: statistical analysis. FL, RG, and MD: methodology. FL and MD: supervision. RG and LZ: writing—original draft. MD, FF, CP, and FL: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Cannabis Use and Neuroadaptation: A Call for Δ^9-Tetrahydrocannabinol Challenge Studies

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Currently, the assessment of the neurobehavioral consequences of repeated cannabis use is restricted to studies in which brain function of chronic cannabis users is compared to that of non-cannabis using controls. The assumption of such studies is that changes in brain function of chronic users are caused by repeated and prolonged exposure to acute cannabis intoxication. However, differences in brain function between chronic cannabis users and non-users might also arise from confounding factors such as polydrug use, alcohol use, withdrawal, economic status, or lifestyle conditions. We propose a methodology that highlights the relevance of acute Δ^9-tetrahydrocannabinol (THC) dosing studies for a direct assessment of neuroadaptations in chronic cannabis users. The approach includes quantification of neurochemical, receptor, and functional brain network changes in response to an acute cannabis challenge, as well as stratification of cannabis using groups ranging from occasional to cannabis-dependent individuals. The methodology allows for an evaluation of THC induced neuroadaptive and neurocognitive changes across cannabis use history, that can inform neurobiological models on reward driven, compulsive cannabis use.

Keywords: cannabis, neuroadaptation, neurocognition, mesocorticolimbic circuit, cannabis abuse

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INTRODUCTION

Cannabis is the most commonly used illicit drug, with 4% of the global population reportedly using the substance (1). The prevalence of cannabis use is expected to increase following recent trends to legalize or decriminalize its use for recreational and therapeutic purposes (2, 3). Thus, as cannabis use increases and the perception of risk of use decreases (4), a pertinent question is how prolonged cannabis use affects the neurocognitive state, and whether there are long-term neurobiological consequences (5). Furthermore, as 10% of those who recreationally consume cannabis develop daily use patterns (6), it is prudent to understand neuroadaptations in the neuro-circuitry which may underlie this increase and persistence of use.

Neuroadaptation in chronic cannabis users has traditionally been evaluated with brain imaging measures in comparison to non-cannabis using controls. Many of these cross-sectional fMRI studies have revealed changes in functional connectivity (7–11), task-related brain activation (12–18) and neurotransmission (19–23) in various brain regions of chronic cannabis users, sometimes in association with cognitive deficits (24–29). However, findings have also been mixed

as these studies suffer from the methodological problem that confounding factors (e.g., pre-existing differences, polydrug use, and differences in lifestyle) cannot adequately be controlled and therefore, in addition to cannabis use, might explain observed differences in brain function (30). Cross-sectional studies between chronic cannabis users and non-cannabis users therefore cannot be taken as the sole approach for studying the effects of repeated cannabis use on brain function and its associated neurocognitive state.

Alternatively, we propose that neuroadaptive changes in cannabis users can more selectively be studied in response to an acute challenge with Δ^9 -tetrahydrocannabinol (THC). Ideally, such studies would follow a multimodal imaging approach that includes resting state fMRI to assess functional connectivity, PET imaging to profile CB1 receptor densities, and magnetic resonance spectroscopy to quantify neurometabolites in neural circuits in which neuroadaptions are prominent, such as the mesocorticolimbic circuit (31) (**Figure 1**). Neural changes to an acute THC challenge should be assessed as a function of cannabis use frequency as there is a notion that neural mechanisms underlying acute and long-term cognitive deficits are interrelated and that the latter can be explained as a neuroadaptive response to the former (32). For example, an acute dose of THC has been found to increase glutamate (33–35) and dopamine (36–39) in the striatum of occasional users, whereas sober chronic cannabis users demonstrate a decrease of glutamate and glutamate-related metabolites (19–22), and lower levels of dopamine release (40, 41). Likewise, fMRI studies have repeatedly shown hypoactivation in the mesocorticolimbic circuit during acute THC intoxication (32, 33, 35) in occasional users but hyperactivation in sober, chronic cannabis users (12, 15–17, 26, 42). The intermediate mechanism might be CB1 receptor density that is known to fluctuate with cannabis frequency and represents a neuroadaptive response of the brain to regain homeostasis following sustained and repeated THC exposure (31). It can be hypothesized that this neuroadaptive response in chronic cannabis users is aimed to normalize cognitive function during THC intoxication, but causes underactivation of brain function when sober (32). The dynamics of this antipodal neural response underlying acute and long-term effects of cannabis can typically be studied in placebo-controlled THC studies as a function of cannabis use frequency as shown in **Figure 2**. This approach could be applied to a number of research issues that are closely associated with cannabis use disorder, as discussed below. These include assessments of neural mechanisms that underlie the progression to compulsive cannabis use, the development of tolerance, and their association to neurocognitive key-elements of addiction such as reward, craving, and cognitive control (43).

TRANSITION TO COMPULSIVE CANNABIS USE

Acute THC studies can be employed to increase or confirm our understanding of the neural and psychological basis of the transition from initial cannabis use to compulsive use. Compulsive cannabis use occurs in parallel to the development of cannabis tolerance but their underlying neural mechanisms may differ. Preclinical studies have suggested that THC-induced dopamine release shifts from the ventral striatum to the dorsal striatum after repeated administration (44), a transition that has been associated with the development of dependence in humans (45). In addiction research, dorsal striatal activation dominance in drug use disorders has been associated with habitual, drug-seeking behavior (43, 46–49), while increased ventral striatal activation has been associated with increased responsiveness to drug-related cues and reward (50–52). Indeed, dependent and non-dependent cannabis users have shown increased responsiveness of the ventral striatum in response to cannabis-related cues (8, 45, 53–56) and increased striatal frontal coupling (45). Dependent users also exhibit increased dorsal striatal reactivity and decreased striatal limbic coupling during cannabis cue exposure (45). Shifts in ventral and dorsal activation as observed in cannabis users are thus intrinsically related to the frequency of acute cannabis intoxications. The development of the striatal response to cannabis cues should therefore also be studied and understood in the context of acute THC challenge studies in groups with varying cannabis use frequencies. Such studies could potentially monitor directly how acute THC intoxication affects ventral-dorsal striatal activation as a function of cannabis use history and further clarify the contributory roles of striatal dopaminergic and glutamatergic neurotransmission to excessive cannabis use and habit formation. The latter is of particular relevance, as a number of acute THC studies have shown that a single dose of THC attenuates the striatal response to rewards such as monetary incentives, cannabis marketing, and music (56–58) suggesting that THC-induced increments in striatal dopamine reduce salience and attentional processing of concurrent rewards (56). Acute THC challenge studies therefore would not only contribute to a fundamental understanding of ventral-dorsal striatal activation with increasing cannabis use, but also provide important pharmacological insights on how shifts in striatal balance can be prevented or controlled in order to avoid progression to compulsive cannabis use.

DYNAMICS OF TOLERANCE AND NEUROCOGNITION

Neurocognitive impairments observed during cannabis intoxication are transient and dynamic over time, depending on cannabis use frequency (31). Understanding the dynamics of tolerance can be useful when trying to "tailor" the cannabis experience and develop dosing strategies which promote tolerance in patient populations where they do not want the "high" and neurocognitive impairment. Alternatively, dynamics of tolerance can also inform strategies to promote efficient "tolerance breaks" for individuals who want the "high" and the associated neurocognitive state, but wish to reduce the potential for addiction, as tolerance development promotes addictive behavior (31, 59).

The neurocognitive state of cannabis users is strongly associated with neuroadaptations in the mesocorticolimbic circuit that occur during acute intoxication, chronic use,

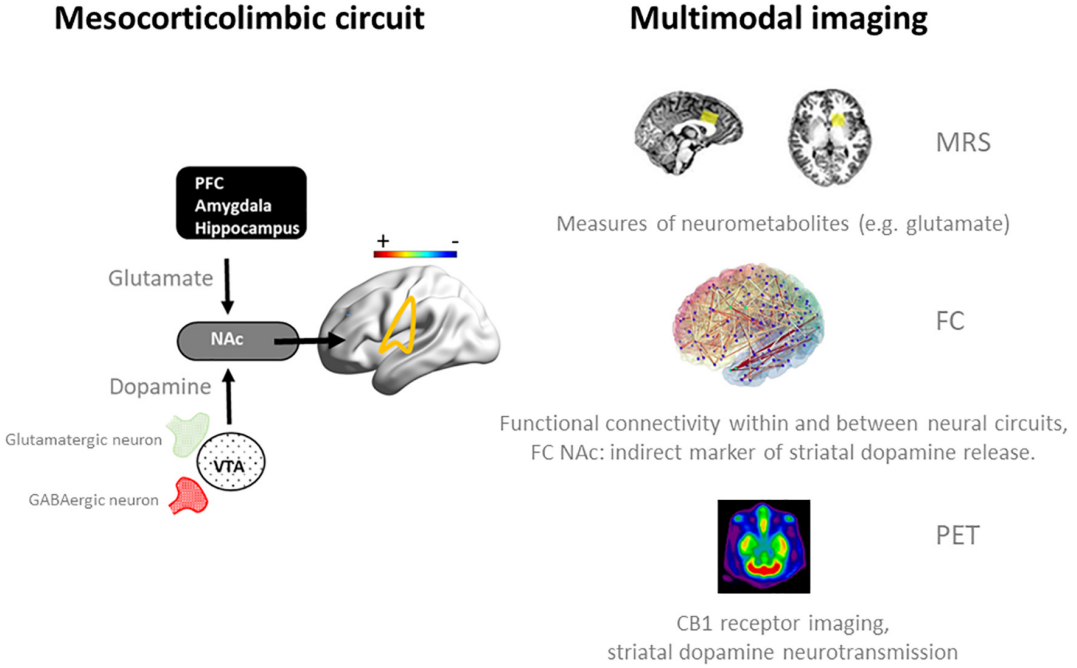

FIGURE 1 | Schematic representation of neurotransmission and functional connectivity in the mesocorticolimbic circuit in the normal brain (32) (left panel) and multimodal imaging measures (right panel) that can be employed to assess dynamics within this circuit during an acute challenge with THC and when sober. Magnetic Resonance Spectroscopy (MRS) has been successfully used to quantify frontal and striatal glutamate concentrations in cannabis users during intoxication and when sober (33, 34). fMRI measures of functional connectivity (FC) have provided functional associations within and between neural networks in cannabis users during intoxication (33, 35, 42) and when sober (15–17, 42), and can be used as an indirect marker of striatal dopamine release during cannabis intoxication (33, 81). Positron emission tomography (PET) can be used to determine CB1 receptor density at glutamatergic and GABAergic neurons in the striatum of cannabis users (60, 62) and to determine dopamine displacement at D2/D3 receptors as a measure of dopamine transmission during cannabis intoxication (36). NAc, nucleus accumbens; PFC, prefrontal cortex.

and abstinence (see **Figure 2**). Chronic exposure to cannabis produces significant downregulation and desensitization of CB1 receptors in cannabis-dependent users relative to that in controls (60–62). This homeostatic response of the brain also potentially causes a state of underactivation and neurocognitive dysfunction in chronic cannabis users when sober (31, 63–65). Typically, such deficits rapidly decrease during abstinence and do not persist beyond 4–5 weeks (63, 66). It has been hypothesized that neurocognitive impairment in chronic users arise from a state of withdrawal during which CB1 receptors are downregulated and restrained from THC-related receptor stimulation (32). Subsequent CB1 receptor upregulation observed during withdrawal in chronic users (60) was indeed paralleled by an improvement in neurocognitive function (64). Interestingly, the only study to date that investigated the neuroadaptive response to an acute challenge in chronic cannabis users (35) suggested that stimulation of CB1 receptors subsequently normalizes striatal glutamate and dopamine transmission, functional mesocorticolimbic connectivity, and neurocognitive function (31, 32, 35). This neuroadaptive response may also explain the absence of neurocognitive impairment (i.e., tolerance) that is often reported in chronic cannabis users during THC intoxication (31, 67).

Neuroimaging studies can be instrumental in assessing the dynamics of CB1 receptor density and neurocognitive state before or after an acute THC challenge in groups of cannabis users who vary in their frequency of use. Such studies could establish downregulation of CB1 receptor density with increasing cannabis use and determine the impact of CB1 downregulation on mesocorticolimbic function and neurocognitive state, in the presence and absence of an acute THC challenge. Increased knowledge of how temporal changes in cannabis use frequency affect the dynamics of an individual's response and neuroadaptations to an acute challenge with cannabis, will gain relevance with increasing recreational and medical use of cannabis. Frequency, dose, and duration of use to achieve or reverse tolerance are currently unknown but are important to define recreational use frequencies and medical dosing strategies at which the development of acute tolerance, persistence of neurocognitive deficits, and compulsive use can be avoided.

MARKERS OF THE NEUROCOGNITIVE STATE

Acute THC studies might also serve to identify neural markers of cognitive function that differentiate compulsive cannabis use from non-problematic cannabis exposure, or the impaired state from the non-impaired state. At present, there is no objective

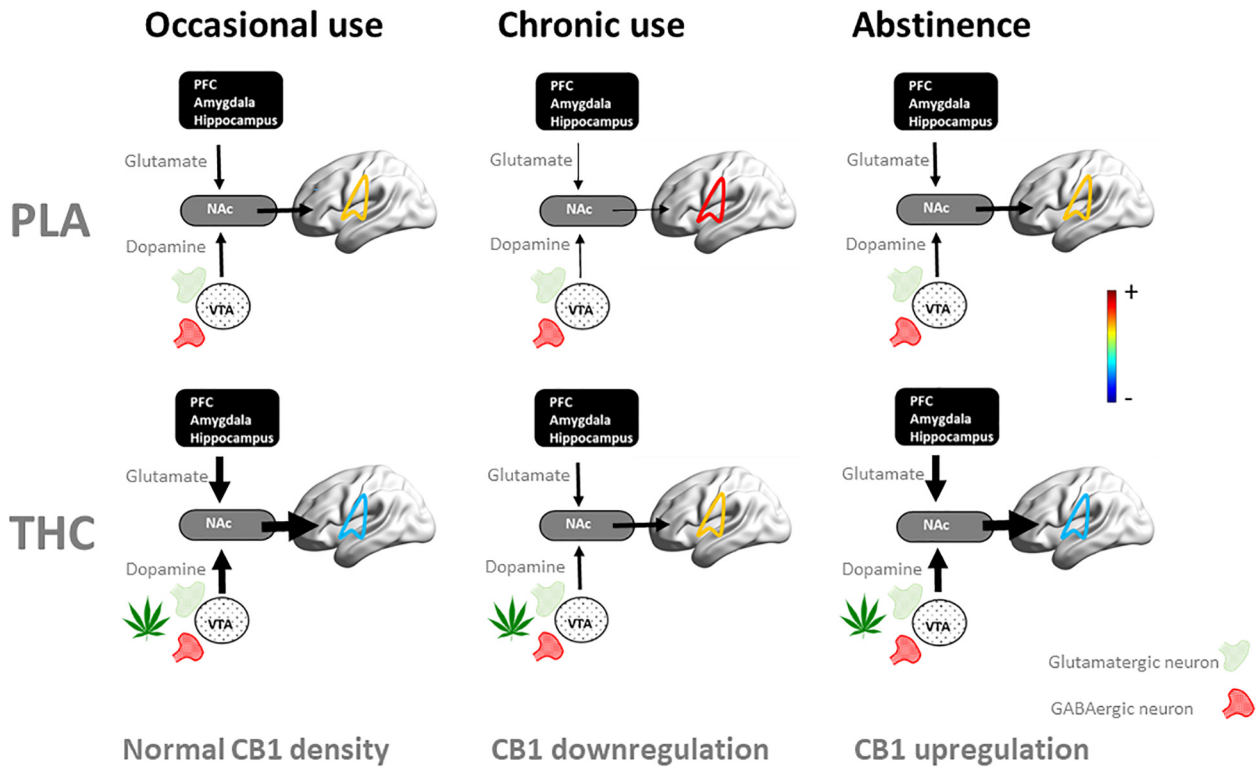

FIGURE 2 | Schematic representation of the dynamics of the neuroadaptive state of the mesocorticolimbic circuit when challenged with placebo (PLA) and THC as users proceed from occasional to chronic cannabis use and into abstinence. In occasional users, an acute THC challenge increases striatal levels of dopamine and glutamate (33–35) through stimulation of CB1 receptors at presynaptic GABAergic and glutamatergic receptors, leading to hypoconnectivity of the mesocorticolimbic circuit (here shown superimposed on brain) and neurocognitive dysfunction (33, 35). With repeated cannabis use, CB1 receptors are downregulated as a neuroadaptive response to CB1 receptor overstimulation (60, 62). In chronic users, this leads to reduced striatal dopamine (40, 41) and glutamate (19–22), as well as hyperconnectivity within the mesocorticolimbic circuit (9, 42, 82) and neurocognitive dysfunction when sober (13, 24, 27, 28). In these users, stimulation of CB1 receptors normalizes striatal dopamine and glutamate concentrations, functional connectivity and neurocognitive function during acute THC intoxication (35). With prolonged abstinence of cannabis, CB1 receptors upregulate (60, 62) and potentially normalize the neuroadaptive and neurocognitive state (63, 64, 66). NAc, nucleus accumbens; PFC, prefrontal cortex.

assessment that can classify the neurocognitive state in individual cannabis users. Recent studies have suggested, however, that acute THC intoxication as assessed by subjective ratings of "high" produces a reproducible signature change in brain function that can be detected with neuroimaging techniques (42, 68). The former study (68) conducted functional near-infrared spectroscopy (fNIRS) in cannabis users before and after receiving oral THC and placebo and found increased oxygenated hemoglobin concentration (HbO) in the prefrontal cortex of participants with a clinical rating of subjective intoxication. Machine learning models using fNIRS time course features and connectivity matrices identified the intoxicated state with 76.4% accuracy (68). The latter study (42) used a data-driven independent component methodology to analyze fMRI resting state data to extract a distinct spatial connectivity pattern of hypoconnectivity involving the dorsal attention, limbic, subcortical and cerebellum networks, and of hyperconnectivity between the default mode and ventral attention network, that was associated with the feeling of a subjective "high" during THC intoxication (42). That same study also revealed a broad state of hyperconnectivity within whole-brain networks in chronic cannabis users compared to occasional cannabis users, which might be reflective of an adaptive network reorganization following prolonged cannabis exposure. These acute THC studies suggest that neural fingerprints of cannabis intoxication and cannabis use history can be derived from neuroimaging data. Future studies with acute THC challenges might identify neurobiological features or phenotype characteristics of impaired and maladaptive behaviors that might arise from acute and chronic use of cannabis. Such models might provide unique insights into emerging adaptations of distinct functional networks in users that progress from occasional to chronic cannabis use and underlie the development of a pathological state, such as cannabis use disorder.

CONCLUDING REMARKS

While the effects of chronic cannabis exposure on brain function and cognition have become a focal point for research, much remains unknown about neuroadaptive responses to acute THC intoxication, and how these develop over time into chronic

cannabis use. This paper posits that pharmaco-imaging studies should be considered to explore how neural responses to an acute THC challenge develop with repeated cannabis use and how such neuroadaptations relate to the development of cannabis tolerance, compulsive cannabis use, and their associated neurocognitive state. Such studies could also target additional factors that are known to moderate the neural response to an acute THC challenge, such a dose, potency, composition, and formulations of cannabis products as well the interaction with underlying pathological states in case of medical use (32). In principle, this approach could also be expanded on to assess neuroadaptations to other drugs of abuse. For example, acute and chronic alterations in neurotransmission and functional connectivity of the mesocorticolimbic circuit have been reported for cocaine (69–71), nicotine (72–76), and alcohol (77–80). The current proposal on how to assess and define neuroadaptations in cannabis users would also call for an international, multi-center research effort in order to include large samples of distinct cannabis user groups, ranging from novice and occasional users at the lowest end of the use frequency spectrum to daily, chronic users at the opposite extreme. It would offer a unique opportunity to develop an integrative, mechanistic view of long-term effects of cannabis on the brain as a neuroadaptive response to acute THC challenges or to the absence thereof.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved its content.

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REVIEW
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Anti-saccade as a Tool to Evaluate Neurocognitive Impairment in Alcohol Use Disorder

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It has been widely shown that chronic alcohol use leads to cognitive dysfunctions, especially inhibitory control. In an extension of the traditional approach, this research field has benefited from the emergence of innovative measures, among which is an anti-saccade, allowing direct and sensitive measure of the eye movements indexing attention bias to alcohol-related cues and the capability of inhibiting the reflexive saccades to the cues. During the past decade, there are numerous reports showing that drinkers make more unwanted reflexive saccades and longer latency in the anti-saccade task. These increased errors are usually explained by the deficits in inhibitory control. It has been demonstrated that inhibitory control on eye movement may be one of the earliest biomarkers of the onset of alcohol-related cognitive impairments. This review summarizes how an anti-saccade task can be used as a tool to investigate and assess the cognitive dysfunctions and the early detection of relapsing risk of alcohol dependence.

Keywords: alcohol use disorder, anti-saccade, cognitive impairment, attention bias, inhibitory control

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INTRODUCTION

Alcohol use has increased rapidly in many countries in the past decade, especially during times of the coronavirus disease 2019 (COVID-19) pandemic, due to the increase in illegal production of alcohol and the disruptions in access to medical care for alcohol dependence (1–3). A substantial body of evidence suggests that chronic excessive alcohol use can cause deficits in a broad range of cognitive functions, including memory, learning, psychomotor speed, visuospatial functioning, attention, executive functioning, and impulsivity (4). A common cognitive mechanism underlying these deficits, alcohol use disorder (AUD), may be the inflexibility of inhibitory control that can be probed with behavioral paradigms such as Stroop task and go/no-go task (5–7).

In the above-mentioned behavioral paradigms, the impaired inhibitory control on the response or attention bias to the substance-related cue was often indexed by lowered accuracy or delayed responses to complete the cognitive task when the cue was presented as distracting information. For example, conflict between task-irrelevant words and task-relevant colors in the Stroop task led to interference on the behavioral response that is required by the task. It can be tested that, relative to neutral cues, drug-related cues induce attention in drug users. The attention bias to drug-related stimuli is reflected by the increase in reaction times (RTs). However, the evidence is indirect and the effect is somewhat circumstantial because the increased RT is affected by complex

cognitive processing as well as linguistic and motor abilities. The assessment of attention bias would be benefitted from multiple dimensions: What was noticed first? How long did it take the subject to attend the target? Was the attention bias due to the difficulty of disengaging attention from the drug-related cue? Addressing these issues thus asks for a direct and multidimensional index and real-time monitoring for attention bias, i.e., eye movement.

The anti-saccade task, first developed by Peter Hallet in 1978, has emerged as an imperative tool for investigating the capacity of suppressing the prepotent response (8). A correct anti-saccade performance consists of two main saccadic processes, namely, restraining a reactive saccade toward the target and then producing a saccade in the opposite direction. In this task, a sudden-onset target appears in the peripheral visual field and participants are instructed to suppress the automatic response (pro-saccade) and instead direct their gaze in the opposite direction (anti-saccade). To carry out volitional saccade in the opposite direction, the powerful urge to make a reflexive response to a sudden-onset target has to be suppressed. This effortful process results in slower latencies for correct anti-saccades and more errors than for pro-saccades.

There are three variants of anti-saccade tasks, namely, gap, overlap, and immediate condition (9). The division of the three paradigms is based on the temporal difference between the disappearance of the central fixation point and the emergence of the target. If the central fixation is still there when the target appears, it is the overlap condition; if the central fixation point has disappeared for a period of time when the target appears, it is the gap paradigm; and if the central fixation just disappears when the target appears, it is the immediate condition (**Figure 1**). It has been suggested that anti-saccade task provides abundant sources of data to study the link among inhibitory control, executive function, and the underlying neural substrates.

In this review, first, we briefly described the neurocognitive impairment in AUD, the potential neurobiological, and neurochemical mechanisms by which alcohol consumption leads to cognitive dysfunctions. Second, we also discussed how the anti-saccade task can be used as an important tool to investigate the capability of suppressing the impulse to the substance-related stimuli in AUD, and how anti-saccade performance can predict the long-term cognitive dysfunctions and the early detection of relapsing risk of AUD.

THE MOST COMMON MEASUREMENTS IN THE ANTI-SACCADE TASK

The commonly used indicators in anti-saccade tasks are as follows (10, 11): (1) saccade latency, also known as RT of the first saccade, refers to the interval from the appearance of the target to the first saccade. In the anti-saccade task, there are correct anti-saccade latency and wrong pro-saccade latency. (2) The wrong rate of saccade direction refers to the proportion of saccades made in the wrong direction in the anti-saccade task. The stimulus suddenly appearing in the visual field induces reflective saccade toward the target, which are otherwise required to be inhibited. Therefore, the direction error rate of saccade can reflect the autonomous control ability and is an important index to investigate inhibition function. In addition, saccade amplitude, velocity, and peak velocity of reverse saccade are also the basic indicators of the anti-saccade task, which can reflect the ability to execute and inhibition control.

NEURAL MECHANISMS OF ANTI-SACCADES

The neural mechanisms of anti-saccades have been extensively studied, and the brain regions responsible for anti-saccades have been identified. In anti-saccade tasks, the automatic saccade (pro-saccade) and the voluntary saccade (anti-saccade) were thought to be in the planned state at the same time. Meanwhile, they have a competitive relationship in the neural activation or inhibition. The outcome of the competition ultimately determines which kind of saccade would be implemented.

Whether or not a correct anti-saccade can be generated depends on the relative activation of the neural system toward a pro-saccade and anti-saccade (12). The competition theory suggests that if the neural system performing anti-saccade reaches the activation threshold first, a correct anti-saccade will be generated and the reflexive saccade will be suppressed (13). Conversely, if the neural system performing reflexive saccade first reaches the activation threshold, it will lead to a false saccade toward the target, and then a corrected saccade may be generated. The process of the anti-saccade is more complex, and its activation threshold is relatively higher than that of a pro-saccade (14). The neural activation of the automatic saccade has to be decreased so that the anti-saccade system can reach the activation threshold.

The superior colliculus (SC) and the frontal eye fields (FEFs) contain distinct populations of fixation and saccade neurons, which play a regulatory role in the production of a correct anti-saccade through modulating discharges in a reciprocal manner (15). Compared with prosaccade trials, activity of fixation neurons is enhanced on anti-saccade trials, which can explain the anti-effect: longer RTs in anti-saccade trials than in pro-saccade trials. The contralateral dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) can inhibit reflexive saccade by inhibiting the neurons (16). Recently, converging evidence in experimental animals and human has revealed the neural networks that are involved in the production of anti-saccades. Clinical studies found that patients with lesions of the DLPFC struggled to perform the anti-saccade task, leading to the suggestion that the frontal lobes played a significant role in the inhibitory control (17). Similarly, by combining iontophoretic application of the general muscarinic receptor antagonist scopolamine with single-cell recordings, Major AJ et al. demonstrated that the blockade of muscarinic receptors in DLPFC led to deficits in saccade and visual direction selectivity measures (18). Johnston, Kevin et al. found that the DLPFC neurons send signals selective for stimulus location, saccade direction, and task directly to the SC through the technique of implanting electrodes in DLPFC and SC (19). These studies

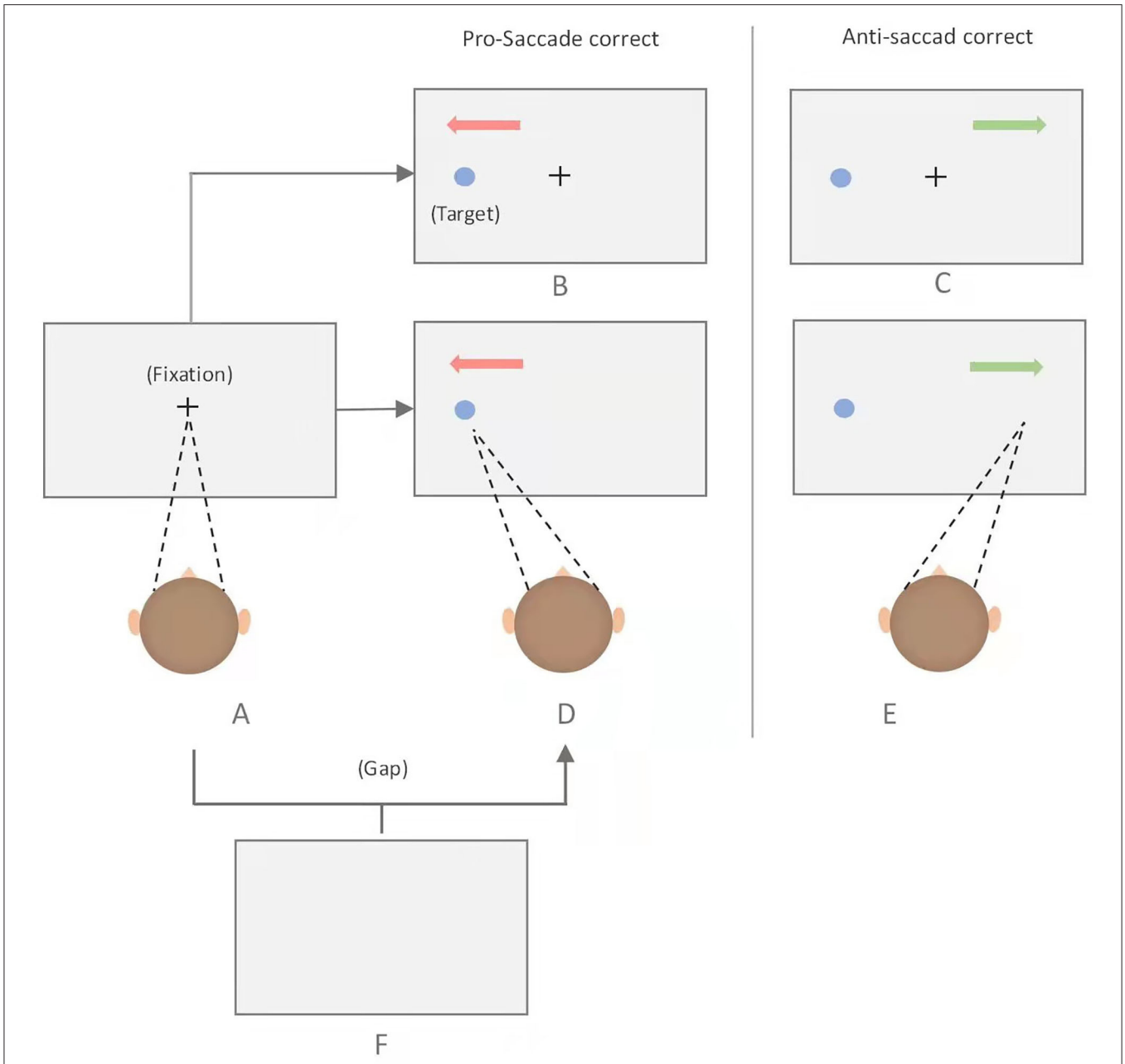

FIGURE 1 | Schematic of the pro- and anti-saccade tasks. Each trial began with the presentation of a fixation point at the center of the screen, which participants are required to fixate, and to make either a prosaccade or antisaccade depending on the task rule. Immediate pro-saccade task: A-D; Immediate anti-saccase task: A-E; Gap pro-saccade task: A-F-D; Gap ant-saccade task: A-F-E; overlap pro-saccase task: A-B; Overlap anti-saccade task: A-C.

have provided evidence that the DLPFC may provide top-down signals to the SC neurons to inhibit the automatic saccade (20). Another area that might also send a supplementary signal to SC and FEF for the motor command of anti-saccades is the supplementary eye fields (SEFs). These commands sent to the brainstem premotor circuit can augment motor commands from the FEF and SC leading to the successful production of volitional anti-saccades (21).

It is more likely that a wrong-directional saccade and correct anti-saccade are not a series of processing processes but rather may be processed simultaneously. The individuals plan the correct anti-saccade while restraining the automatic pro-saccade. There is a certain connection between the parietal lobe region of the brain and the spatial calculation of an anti-saccade. The tasks require the perceptual motor conversion function to transform the visual stimulus into the appropriate motor command for the

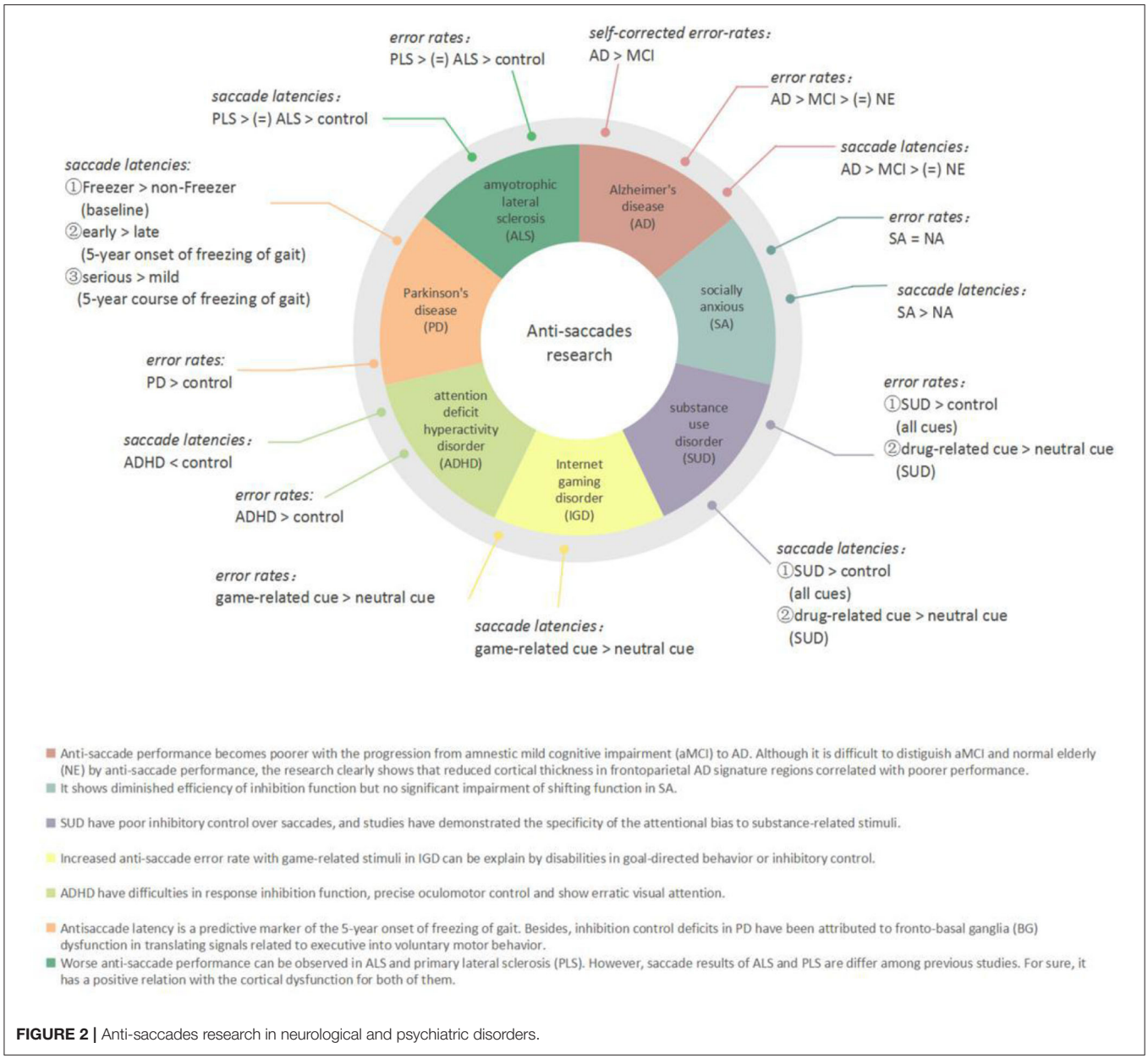

FIGURE 2 | Anti-saccades research in neurological and psychiatric disorders.

execution of saccades of the parietal lobe. The conversion is fast and the exact mechanism is unknown. However, evidence has accumulated to the lateral intraparietal area (LIP), and FEF might have a crucial role in vector inversion (22).

Anti-saccades Research in Neurological and Psychiatric Disorders

Eye movement plays a vital role in the acquisition of visual information. Eye movement tasks, especially saccadic tasks, have been widely used in patients with neurological and psychiatric disorders to assess cognitive function in recent years (**Figure 2**). Holden et al. believed that it was a dynamic process for patients to develop from amnestic mild cognitive impairment (aMCI) to Alzheimer's disease (AD). According to this point of view, they conducted anti-saccade tasks among three groups (i.e., aMCI, mild AD, and controls), which found that patients with aMCI committed significantly more anti-saccade errors (46.9%) compared with those of controls (24.3%). Moreover, the AD group had a significantly larger self-corrected error rate than the other two groups (23). The anti-saccade task is especially useful for detecting dysfunction in selective attention in aMCI and AD (24). In some other studies, participants with AD showed reduced activation in the FEFs and posterior cortex and increased inhibitory errors when performing the anti-saccade tasks in a functional magnetic resonance imaging (fMRI) study (25). Executive dysfunction can be tested in Parkinson's disease (PD); Gallea C et al. investigated the predictive factor of freezing in PD by anti-saccade tasks and reported that compared with the

non-Freezer group, the Freezer group showed equivalent motor or cognitive signs but increased anti-saccade latency before the impairment of motor or other cognitive function like memory. They concluded that anti-saccade latency is a predictive marker of the 5-year onset of freezing of gait (26). Moreover, inhibition control deficits in PD have been attributed to fronto-basal ganglia (BG) dysfunction in translating signals into voluntary motor behavior (27–29). Saccadic data also confirmed executive dysfunction in amyotrophic lateral sclerosis (ALS) as the higher percentage of direction errors in the anti-saccade tasks and increased saccadic latency (30).

Anti-saccade tasks are also used in psychiatric disorders to assess inhibitory control and explore the potential neurobiological mechanisms of the diseases. Children with attention deficit hyperactivity disorder (ADHD) exhibited shorter latency and significantly a higher anti-saccade error rate than the control group, which confirmed that children with ADHD have difficulties on precise oculomotor control and oculomotor response inhibition function (31). This kind of oculomotor control dysfunction is reflected in patients with internet gaming disorder (IGD) and socially anxious (SA). The IGD group exhibited higher saccade-error rates in the case of game-related images than in neutral or scrambled images (32). However, SA participants had longer anti-saccade latencies than non-anxious (NA) participants (33).

NEUROCOGNITIVE IMPAIRMENT IN AUD

Alcohol Effects on Cognitive Function

Alcohol consumption can lead to impaired cognitive functions, accompanied with an impulse to substance-associated stimuli (34). The ability of inhibiting an automatic impulse can be indexed by the Stroop effect that assessed with the computerized version of the Stroop Color and Word Test (SCWT) (35). It is widely believed that the Stroop test is one of the gold standards of attention measures and one of the most popularly used instruments in clinical and experimental neuropsychological settings (36). In the SCWT, participants are often presented with colored color words (e.g., the word "red" printed in green) and are required to suppress the dominant tendency to read the word and instead identify the print color of the word, e.g., green) (37). The extent to which the print color is correctly and quickly identified is taken as how well the distracting word is inhibited. It has been found that patients with AUD show longer RTs in color-naming words and higher error rates on alcohol-related Stroop pictures (i.e., photos of alcoholic drinks or persons drinking alcohol) than neutral Stroop pictures (i.e., photos of kitchen items or persons in kitchen scenes), indicating an attention bias to alcohol cues relative to neutral cues (38–40). In addition, Christiansen and his colleagues showed that including individualized stimuli (e.g., the current participant's favorite drink) as the Stroop stimuli is more sensitive to measure the attention bias than including standardized stimuli (41). Studies using different paradigms, such as go/no-go tasks (42–44), visual conjunction search (VCS) tasks (45), cued visual probe tasks (cVPT) (46), and flanker tasks (47) and have consistently demonstrated that participants with AUD showed attention bias to alcohol-related cue. Moreover, these experiments also indicated that the poorer behavioral control was related to higher alcohol consumption.

In addition to attention bias and impaired executive function, AUD also showed other cognitive deficits. For instance, individuals drinking more frequently showed worse performance in a visuospatial functioning task, and this effect did not depend on more alcohol use days (48). By examining changes in working memory performance as measured by Trail Making Test-B, Lechner et al. highlighted that the function between greater alcohol-induced working memory decline and adverse consequences was mediated by the amount of the drinks per drinking day (49). However, Nguyen-Louie et al. drew a contrary conclusion about the link between adolescent alcohol with neuropsychological measurements, showing that more alcohol use days led to more neurotoxic events, and predicted worse verbal memory, visuospatial ability, and psychomotor speed, whereas unexpectedly, predicted better working memory performance (50).

Alcohol Effects on the Brain Structure

The long-term, heavy consumption of alcohol results in reversible or irreversible modification of selective neural systems of the brain function and structure (51, 52). Brain structure damage in chronic alcoholism is well documented (53). Based on modern neuroimaging technology, an increasing number of studies have shown brain structure damage that can be related to alcohol dependence.

For example, Cosa et al. found robust magnetic resonance imaging (MRI) markers that are affected by alcohol, which showed the sensitivity and selectivity even after the relative short exposure period of alcohol consumption (54). Many animal and human models consistently demonstrated that the prefrontal cortex (PFC) is affected by chronic alcohol consumption. Extensive evidence from neuroimaging studies indicates that alcohol exposure leads to the degradation of circuitry originating from the PFC, which plays an essential role in PFC-dependent behavioral deficits in AUD (55). By using fMRI, Kreusch et al. found greater activation of PFC, in the presence of alcohol-related cues compared with neutral cues in young heavy drinkers (HDs). A potential vicious cycle was suggested that a late maturing of PFC can also increase the vulnerability of developing substance use disorder later in life including AUD (56). The DLPFC, known for its importance in cognitive function, is thought to be impaired globally by alcohol consumption.

To date, an increasing number of studies have addressed anti-saccade performance in AUD. The various forms of behavioral change in AUD show a striking similarity to that of patients with prefrontal lesions, such as AD (57). Hence, anti-saccade task performance is related to structural alterations in the frontal lobe and can be a reliable and valid biomarker for the diagnosis of AUD (58, 59).

ANTI-SACCADE RESEARCH IN ALCOHOL USE DISORDER

Dose Correlates

The impairment of impulse inhibition in AUD has been shown in previous studies using anti-saccade tasks. Specifically, a decreased

anti-saccade accuracy and a specific alcohol-induced impairment in saccade amplitudes were observed in AUD (60–62). Roche DJ et al. investigated how the doses of alcohol consumption affect the eye-movement control. A total of 138 non-alcoholic social drinkers, with self-reported positive (FH+) or negative (FH–) family history, were enrolled in this study. They were divided into two groups [i.e., HDs and light drinkers (LDs)] according to the guidelines from The Substance Abuse and Mental Health Services Administration (SAMHSA). Both groups received eye-movement tests of smooth pursuit, prosaccadic, and antisaccadic task at baseline, 60 min (T1), and 180 min (T2) after the initiation of beverage consumption (63). All the subjects consumed a high alcohol dose (0.8 g/kg), a low alcohol dose (0.4 g/kg), or a beverage containing placebo (1% ethanol as taste mask) with the order randomized across separate sessions. In the anti-saccade tasks, both high dose of alcohol (0.8 g/kg) and low dose of alcohol (0.4 g/kg) increased the latency and decreased anti-saccade velocity for both HD and LD, whereas the effect of high dose was greater and more lasting. Interestingly, HDs reported less perceived deficits from alcohol than LDs in anti-saccade tasks.

It is generally considered that heavier drinkers display reduced reactions to a dose of alcohol. The theory of behavioral tolerance to alcohol posits that more experience with drinking to intoxication leads to less impaired cognitive and psychomotor performance (64). One possible explanation is that exposure to heavy or binge drinking may produce behavioral tolerance to the response to alcohol (e.g., greater motor skills). However, some research explained that behavioral tolerance in heavy drinkers occurs only at the early phase, but the heavy drinkers remain at risk in alcohol harm as they continue to engage in chronic binge drinking over time (65, 66).

Comorbidities Correlates

Alcohol use disorder often shows attention bias to alcohol images, as revealed by eye-tracking tasks (67). The seek for alcohol significantly develops an attention bias, which has been demonstrated in previous studies (68). This effect also can be observed in the populations with co-morbid AUD and other impulse control disorders. Some research has measured the performance in these patients, and the underlying connection between AUD and the comorbidities could be probed with anti-saccade tasks.

Patients with binge eating disorder (BED) show dysfunction of inhibition on response to food cues in anti-saccade tasks, and they usually have co morbidity with AUD and meanwhile show strong impulse to alcohol cues (69–71). Drinkers may have difficulties in inhibiting saccades toward appetitive stimuli, particularly when stimuli were in the peripheral visual field (72). To assess the difference between the deficits of response inhibition between the two disorders, Schag, Kathrin et al. compared the performance between BED, AUD, and their age- and sex-matched control groups in the modified anti-saccade tasks (73). In the tasks, the stimulus in each trial was specific to the disorder (food stimuli for BED and alcohol stimuli for AUD). The results showed that BEDs made more directional mistakes in both first saccades and second saccades, which indicated that BEDs have more difficulties in inhibiting the response to stimuli regardless of the stimulus category. However, AUDs showed no discrepancy in the error rates, compared with the control groups. In addition, AUDs also performed significant less fixations to alcohol stimuli and shorter dwell times on both alcohol stimuli and neutral stimuli in free exploration tasks. Taking the two tasks into consideration, we can suggest that AUD avoid stimuli deliberately. One of the limitations of the research was that AUDs were told to be abstinent before the tasks, so that the tendency to avoid alcohol stimuli can be explained by learning efficiency. Peña-Oliver et al. investigated the diverse degrees of impulsivity to food incentives and substantiated a remarkable increase of goal-directed behavior to food incentives in alcohol-preferring rats, which might be related to their intense preference for alcohol (74). Moderate drinking can increase subsequent food intake, particularly of high-fat savory food as well (75). Christiansen P et al. investigated the effects of alcohol on energy intake and found that individuals who were given an alcohol prime (i.e., alcoholic drink mixed with diet lemonade) (0.6 g/kg) performed worse on the Stroop test and consumed more cookie calories than individuals who were given the placebo drink (76). However, the increase in energy intake was not observed in acute alcohol consumption (0.4 g/kg) in another study (77). Recent research demonstrated that alcohol consumption can increase food intake and food reward, but such effects occur only at a higher dose (0.6 g/kg) (78). A conclusion that can be drawn is that, in anti-saccade tasks, patients with BED show unselected attention bias to food cues (including alcohol-related stimuli), whereas only patients with AUD with low dose of alcohol show highly selective attention bias to alcohol-related cue. The attention bias to alcohol-related stimuli in AUD may generalize into food cues when the patients consume more alcohol.

In another line, researchers have examined the dysfunction of impulse control in patients who had comorbid alcohol and cocaine use disorder. They concluded that the anti-saccade performance could be a predictor of decreased white matter integrity (79). Given that anti-saccade performance affected by alcohol intoxication has been shown in different forms of comorbidity with AUD, the task may have the ecological validity in the way that it can be a promising tool to assess the risk of further developing into other impulse control disorder with the long-term alcohol consumption.

Alcohol Intoxication

The development of AUD involves chronic heavy drinking to high levels of alcohol intoxication. Likewise, earlier occurred alcohol intoxication in adolescent is related to the higher rate of diagnosing AUD in the adulthood (80, 81). In addition to long-term neurocognitive impairment, some research has focused on the deficit of inhibition control during intoxication period with behavioral paradigm. In a study using the Stroop task, 20 healthy social drinkers, who reported imbibing 1–3 times a week as light-to-moderate drinking pattern and 1.5–3.5 drinks an occasion, participated in both alcohol (vodka as 20% v/v in orange juice) and placebo (the same volume of orange juice)

sessions as their own control condition. The modified four-color Stroop task required individuals to respond to the color. Each word's color was consistent or inconsistent with the word meaning. There were also trials with a word in gray color, and the participants had to respond to the word meaning. Blood oxygen level-dependent (BOLD) signal was acquired using fMRI during the task. The results showed that alcohol increased RTs error rates in incongruent trials. Moderate alcohol inebriation attenuated ACC activation during both incongruent trials and erroneous responses. These findings suggested that alcohol consumption interferes with goal-directed behavior, resulting in poor inhibition control.

The Stroop evidence based on the behavior results is somewhat indirect. The cognitive processes include in such tasks involve both manual inhibition and saccade inhibition. Alcohol can also affect the motoric execution, such as the button press (82).

Anne Eileen Campbell et al. investigated the effect of alcohol on response control separately. In their study, 40 participants reported consuming 48 g ethanol in one session on at least 6 occasions in the past year, and they were required to complete each experimental task in sessions before and after drink manipulation in the alcohol testing day (i.e., 40% volume vodka in 500 ml orange juice) and placebo testing day (i.e., the same volume of orange juice with a few drops of vodka). The task can be divided into two parts, namely, manual and saccadic stop-signal reaction time (SSRT) task (83). In manual SSRT tasks, participant are told to make rapid responses with right or left index fingers to the location of the target. Similarly in saccadic SSRT tasks, saccades are produced corresponded the left and right targets. In addition, a red fixation point appears in the center of the screen as a distraction in 25% trials, and participants completed these trials with the instruction to ignore the signal and continue to make a correct button press or saccade response. The results showed that the RT (i.e., latency) reflecting manual inhibition increased during alcohol intoxication, but the RT (i.e., latency) reflecting saccadic inhibition did not increase. Their finding is different from the previous one, which noted significant increase of saccade latency by alcohol and decrease of peak velocity in classical anti-saccade tasks (61). However, both have found that saccadic error rates were not influenced by alcohol intoxication.

Below, we explained what accounts for the discrepancy in the results between the two experiments. First of all, Anne Eileen Campbell et al. employed the saccadic SSRT task in which reflexive eye movements toward sudden-onset distractive fixation point has to be inhibited but in the absence of the requirement to perform an immediate anti-saccade, which involved vector inversion and voluntary movement. Moreover, the research based on the classical anti-saccade task also detected the impairment of saccade amplitude (accurate mirrored saccadic location) under alcohol. Combined with the above results, it suggests that alcohol intoxication impairs the process of vector inversion and voluntary movement in anti-saccade but not the trigger to inhibit the flexible saccade. Second, in the saccadic SSRT task, the peripheral target appeared 12° from center (6° in anti-saccade task). Nevertheless, the latency of the corrective anti-saccade decreased with increasing stimulus distance (84). This may explain why there was no increase of saccade latency in saccadic SSRT task.

It seems that saccadic inhibition is immune to alcohol intoxication. It has been shown that the frontal cortex and SC are considered to be the key regions and command producers of saccade, respectively. On account of previous studies on the neural mechanisms of antisaccades, the immunological effect probably was due to the interactive regulatory unbalance of fixation and saccade neurons in FEF and SC (15). The saccade neurons (active in prosaccade) are inhibited more intensively than fixation neurons affected by alcohol intoxication so that the visual response that is initiated by the appearance of the target will not exceed reflexive saccadic threshold (20). However, exposing to ethanol has an effect of suppressive cortical visual event-related potentials (ERPs), which then interferes the assessment of inhibitory function in the frontal cortex. Research based on fMRIs results also demonstrated alcohol-induced activity decreases to voluntary anti-saccades and responses to erroneous responses in dorsal ACC, an area that is the central node in a predominantly frontal cortical network sub-serving inhibitory tasks (85).

LIMITATIONS AND FUTURE DIRECTIONS

Although a large number of studies have used anti-saccade tasks, these studies are not uniform in experimental settings. For example, the target eccentricity used in many studies ranges from 4° to 10°, which makes saccade latencies and error rates of different studies inappropriate to compare with each other. The history of alcohol consumption is also a significant factor in the analysis of the ethanol effects on PFC and SC. Thus, it is not conclusive to summarize the extent of impairment of inhibition control among AUDs. In addition, saccade latency and saccade error rate are frequently used in assessing AUDs, but there are relatively few studies on saccade spatial accuracy and the underlying mechanisms. This is also the content to be paid attention to in future research. In preparation for our manuscript, we have searched the databases PubMed, Cochrane library, and Web of Science up to and including October 2021 to collect the literature. Our search terms included alcohol use disorder OR alcohol dependence OR alcoholism OR alcohol intoxication AND anti-saccade OR saccade OR eye-tracking with no search limits applied. However, the relevant literature is not enough for a systematic review. First, these studies involved a wide range of subjects including abstainers, social drinkers, and alcohol intoxication. It is difficult to compare their impaired performance in anti-saccade task given the major discrepancy of inclusion criteria. Second, the different eccentricity of target stimulus could also make a significant impact on the results based on anti-saccade tasks. Finally, according to previous research, the alcohol-related stimuli could lead to an obvious deficit of saccadic inhibition control in AUD compared with the

neutral stimuli. Nevertheless, the studies we searched adopted different types of cue in the tasks and assessed different ability of inhibition control (i.e., manual or saccadic), which are not appropriate for conducting a systematic analysis. Considering all things, we still think it is necessary to summarize these studies to remind the readers that the anti-saccade task is multidimensional, objective, and convenient, as a tool to assess the attention bias and inhibition control in AUD. Moreover, this is our objective to write the review, and we all hope to lay a foundation of diversified research method in AUD in the future.

In summary, as prolonged alcohol abuse is known to impair response inhibition, alcohol abusers may benefit from interventions that improve response inhibition, thereby restoring inhibitory control over automatic impulses (43, 86). Eye-movement tasks, especially the anti-saccade task, may be favorable for detecting the early impairment of inhibitory control and the risk of AD. Some new techniques such as virtual reality (VR) technology and mobile devices can be applied to assess saccadic eye movements in situations more similar to the real world (87, 88). A growing consensus that AUD and AD share common disease pathophysiology is the dysfunction in the cholinergic system in the brain, which probably can explain the preclinical abnormity showed in anti-saccade tasks (89, 90). According to this, the acetylcholine esterase (AchE) inhibitors may improve the frontal executive function in AUDs. Clinicians should also be cautious about the exposure of the social drinkers to the different types of alcohol-related stimuli during anti-saccade tasks, such as alcohol-related auditory cues (91).

These findings, taken together, indicate a new direction in future work. Aided by the early detection of inhibitory error rates in the anti-saccade task, there is increased potential for commencing effective interventions earlier for AUDs.

AUTHOR CONTRIBUTIONS

YS collected the data and wrote the initial draft of the review. LW and MZ did the analyses and revised the manuscript. All authors contributed to the article and approved the submitted version.

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A Comparison of Acute Neurocognitive and Psychotomimetic Effects of a Synthetic Cannabinoid and Natural Cannabis at Psychotropic Dose Equivalence

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Due to differences in potency, efficacy, and affinity for CB1 receptors, similarities and differences in psychoactive effect profiles of natural cannabis and synthetic cannabinoids (SCs) cannot reliably be derived from equipotent dose comparisons. Instead, the current study proposes to compare the intrinsic psychoactive effects of natural cannabis (THC) and an SC, JWH-018, at psychotropic dose equivalence. Participants from two placebo-controlled studies were matched for their levels of subjective high to compare neurocognitive and psychotomimetic effects of THC and JWH-018. At equal subjective intoxication levels, both drugs impaired psychomotor, divided attention, and impulse control, with no significant difference between the two drugs. Both drugs also caused significant psychotomimetic effects, but dissociative effects were considerably more pronounced for JWH-018 than THC. We conclude that psychotropic dose equivalence provides a uniform approach for comparing the neurocognitive and psychotomimetic profiles of CB1 agonists, which can also be applied to other drug classes.

Keywords: cannabinoids, THC, JWH-018, psychotropic dose equivalence, neurocognitive effects, psychotomimetic effects

INTRODUCTION

The availability of novel psychoactive substances (NPS), which mimic the effects of traditional drugs of abuse, has increased rapidly over the past decades (1). NPS include diverse classes of substances, such as synthetic cannabinoids, synthetic cathinones, phenethylamines, piperazines, tryptamines, aminoindanes, and NPS opioids (2). Although NPS use is less common than the use of other illicit drugs (3), the harm caused to individuals can be quite serious, ranging from acute impairment and adverse effects, to drug addiction (1).

One class of NPS, synthetic cannabinoids (SCs), includes compounds initially designed since the 1970's by researchers to investigate the cannabinoid system and to explore new therapeutic indications, e.g., pain disorders and cancer (4, 5). However, in the early 2000s, these compounds (e.g., JWH-018) appeared in smoking mixtures, such as Spice or K2, which were advertised as "natural" alternatives for cannabis. These smoking mixtures became popular rapidly, especially in countries where recreational use of cannabis was illegal or in situations where users wanted to avoid

detection in routine drug screening (6). However, it also became clear from anecdotal reports that these SCs come with serious side effects, such as agitation, psychotomimetic effects, and cardiac events (7–10), as well as fatalities (11, 12). As a result, more and more of these SCs were added to the list of controlled substances in progressively more countries. In response to these bans, the content of the smoking mixtures has changed continuously, with new and more potent SCs being released on the market at an increasing speed (13–15).

SCs bind to the central cannabinoid receptors (CB1 and CB2), which are also the target receptors for Δ9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis. However, the effects elicited by most SCs are more powerful than the effects of natural cannabis (16). The risk of emergency medical treatment is about 30 times greater following the use of SCs than following cannabis (17), with tachycardia, agitation, and nausea as the most frequently reported adverse events (8). Cases of SC intoxication often display cognitive impairment (16). Compared to natural cannabis users and non-cannabis users, frequent SC users were found to perform worse on cognitive tasks, including working memory, inhibition, and long-term memory (18). The most well-known adverse effects linked to SCs are probably psychological symptoms, including agitation, anxiety, and psychosis (16, 19). Psychotomimetic and dissociative effects, often referred to as "zombie effect," have been noted in up to 28% of the people who admitted using an SC (20, 21). Although the symptoms of SCs overlap with those of cannabis, the stronger and more unpredictable effects of SCs cause the majority of users to express a preference for natural cannabis (22).

Most SCs have a specifically high affinity for CB1 (16, 23–26). Furthermore, they act as agonists with high efficacy (i.e., act as a full agonist) (23, 24, 27). This is in contrast to THC, which has low efficacy, low affinity for CB1, and is less potent, and thus is not able to stimulate cannabinoid receptors to the same degree as SCs (24, 28). Consequently, the behavioral effects of a given dose of an SC are not simply comparable to those of an equivalent dose of THC. In pioneering studies conducted in our lab with an early SC, JWH-018, we demonstrated that a low dose produced significant psychomotor and cognitive impairment, as well as psychotomimetic symptoms (29–32) even at subjective intoxication levels that were lower than what is normally reported for natural cannabis. It seems therefore appropriate to take the level of subjective intoxication into account when establishing the psychotropic dose equivalence between an SC and natural cannabis.

In the present manuscript, we defined psychotropic dose equivalence as the dose at which an identical level of subjective high is achieved with an SC and natural cannabis. Subsequently, we aimed to compare neurocognitive and psychomimetic effects of an SC (i.e., JWH-018) and cannabis in participants from two previous placebo controlled studies (31–34) that were matched for their levels of subjective high. We expected that a comparison at psychotropic dose equivalence would allow for an objective comparison of the neurocognitive and psychotomimetic profiles of JWH-018 and THC.

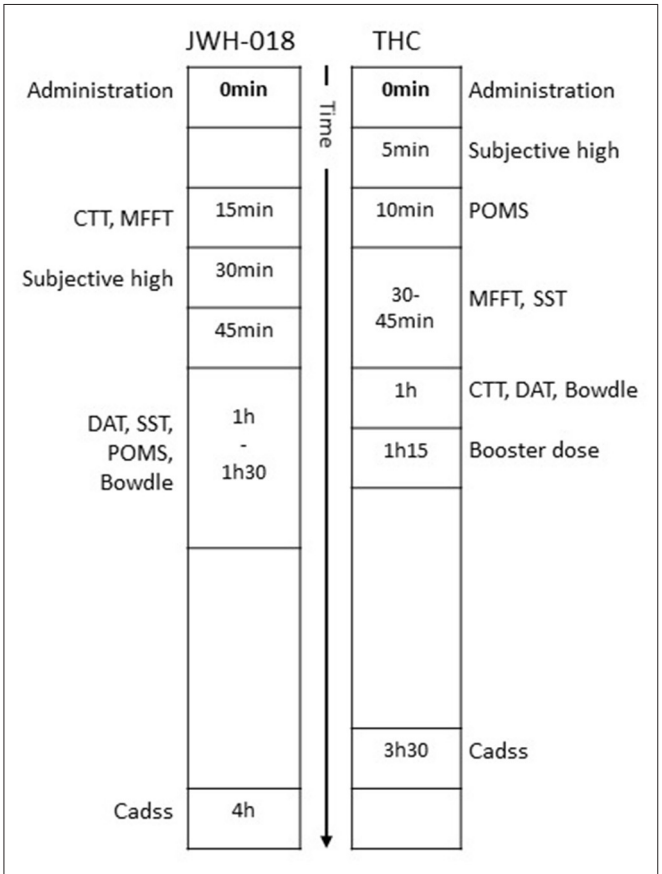

FIGURE 1 | Timeline of subjective questionnaires and cognitive tests relative to time of drug administration.

MATERIALS AND METHODS

Subjective and performance data analyzed in this study comes from two studies with a comparable design and setup (31–34). Both studies were placebo-controlled, cross-over studies examining the acute effect of either cannabis (THC) or JWH-018 in healthy cannabis users. The type of cannabis users was comparable in that both studies included occasional users (i.e., cannabis use between 8 and 120 times/year). The studies used the same test battery and questionnaires to measure cognitive and subjective effects that were administered within a similar time window relative to drug dosing. A summary of the subjective and objective tests applied in both studies, and at which time after dosing they were administered, is provided in **Figure 1**.

Samples and Matching

THC Study

THC data was taken from a previous study from our group (33, 34). In this randomized, double-blind experimental study, 122 cannabis-experienced (at least 8 times/year) participants received 450 μg/kg THC (cannabis plant material, divided into two doses of 300 and 150 μg/kg; i.e., 21 and 11 mg for a 70 kg person), cocaine, and placebo on three separate test days. Cannabis treatment was split into two doses, with the second one

given 1 h after the first dose. Cannabis was prepared from batches containing 11–12% THC, while placebo cannabis consisted of Knaster Hemp. Cannabis and placebo were administered using a vaporizer (Volcano) which heated the materials to a temperature of about 225 °C, while storing the vapor in a polythene bag equipped with a valved mouthpiece. Subjects were instructed to inhale according to a standardized manner, inhaling deeply and holding their breath for 10 s after each inhalation. The bag had to be emptied completely, taking about 2–3 min. Subjective and performance measures were taken within 3.5 h after the first administration (see **Figure 1**). The cocaine condition has been omitted from the current study.

JWH-018 Study

Subjective and performance data after an acute dose of JWH-018 was taken from a previous study performed by our group (31, 32). In this placebo-controlled, cross-over study, 24 healthy occasional cannabis users inhaled the vapor of 75 μg JWH-018/kg body weight and placebo on two separate test days (i.e., 5.25 mg for a 70 kg person). Placebo consisted of Knaster Hemp (Zentauri, Germany), a herbal blend with hemp aroma (0% THC). Both treatments were administered *via* a vaporizer pen, which heated the materials to ∼380°C. Participants inhaled the vapor in five intakes, according to a strict inhalation regimen. A booster dose of 50 μg JWH-018/kg body weight was administered in case participants did not show a subjective response (i.e., a minimum subjective high score of 30% was required) within 15 min after administration of JWH-018. Performance and subjective measures were taken in the 4 h following drug administration (or booster in case needed) (**Figure 1**). Subjective intoxication was measured regularly after JWH-018 treatment but was maximal at 30 min post drug.

Subjective Intoxication

Subjective high was self-rated on a 10 cm Visual Analog Scale (VAS), with 0 indicating "not high at all," and 10 indicating "extremely high." Participants reported their highest scores within the first hour after administration for both THC and JWH-018, followed by a return to baseline levels in the following hours (32, 35, 36). In the THC study, subjective high score was determined 5 min after the first administration, when subjective intoxication for THC was maximal in occasional users (36). In the JWH-018 study, subjective intoxication was maximal at 30 min post drug.

Matching

To ensure comparable cannabis use patterns across the samples, only participants who used cannabis a maximum of 10 times/month were included from the THC and JWH-018 study. Subsequently, participants with a comparable subjective high score after THC or JWH-018 were selected (max, mean, SD difference was 0.8, 0.28, and 0.36). This resulted in 24 participants of the THC sample who could be matched to the participants in the JWH-018 sample. The characteristics of both samples are shown in **Table 1**.

TABLE 1 | Demographics of the participants in the THC and JWH-018 sample.

	THC ($N = 24$)	JWH-018 ($N = 24$)
Male/female	20/4	10/14
	Mean (SD)	***Mean (SD)***
Age (years)	21.95 (4.0)	22.8 (3.05)
Subjective high score (cm)	6.46 (2.0)	6.41 (1.9)
Estimated cannabis use (times) in the month	5.5 (2.5)	3.4 (2.3)

Performance Measures

Critical Tracking Task

The CTT is a psychomotor test that assesses the participant's ability to control a displayed error signal in a first-order compensatory tracking task (37). Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements null the error by returning the cursor to the midpoint. Total duration of the task is ∼3 min. The frequency at which the participant loses control is the critical frequency or lambda-c (λ_c). The test included five trials, of which the lowest and the highest score were removed; the average of the remaining scores is taken as the final CTT-score. This test has repeatedly been shown to be sensitive to the effects of many sedative drugs, including cannabis (36, 38–40).

Divided Attention Task

The DAT measures the ability to divide attention between two tasks performed simultaneously (41). Participants have to perform the same tracking task as described above, but now at a constant difficulty level. As a secondary task, the subject monitors 24 single digits presented in the corners of the computer screen. The participants have to react to the target number "2" by removing their foot as fast as possible from a pedal switch. Duration of the task is 12 min. The mean absolute tracking error (in mm) and the number of control losses are the performance measures of the primary task. The number of misses, false alarms, and mean reaction time (msec) of the responses to the target number, are the performance measures in the secondary task. Performance in this test has proven to be sensitive to the effects of many sedative drugs (36, 38–40).

Stop Signal Task

The SST measures motor impulsivity, which is the inability to inhibit an activated or pre-cued response leading to errors of commission. The current test is adapted from an earlier version (42) and has been validated for stimulant and sedative drug effects (43). The task requires participants to make quick responses to visual go-signals and to inhibit their response if a subsequent visual stop-signal, i.e., "*", appears in one of the four corners of the screen. Total task duration is ∼8 min. Dependent variables are go reaction time (ms), stop reaction time, number of correct responses, omission (not responding on go-trials), and commission errors (not inhibiting a response to a no go trial). Stop reaction time represents the estimated mean time

required to inhibit a response. Stop reaction time is calculated by subtracting the stop signal delay from the reaction time on go-trials associated with n^{th} percentile of the reaction time (RT) distribution (44).

Matching Familiar Figures Test

The MFFT measures reflection impulsivity, which is the tendency to reflect on the validity of problem-solving under the particular condition of several possible alternatives. The test involves simultaneous presentation of a target figure positioned on the left of the screen and an array of six alternatives on the right half of the screen, all except one differing in one or more details from the target figure. The participants are asked to select from the alternatives the figure that exactly matches the target figure as quickly as possible. Task duration is ∼5 min. Two dependent measures, mean latency to first response (ms) and the total number of errors, are automatically recorded. In addition, an impulsivity score (I-score) is calculated by subtracting the standard score of the mean latency to the first response from the standard score of the total number of errors committed. An efficiency score (E-score) is calculated by summing the standard score of the mean latency to the first response with the standard score of the total number of errors committed.

Subjective Measures

Clinician Administered Dissociative States Scale

The Clinician Administered Dissociative States Scale (CADSS) (45) comprises of 19 self-rated items, ranging from 0 "not at all" to 4 "extremely." It is divided into three components: *depersonalisation* (5 items), *derealisation* (12 items), and *amnesia* (2 items). A total dissociative score is achieved by summing all items. The CADSS is designed to be a standardized measure of present-state dissociative symptomatology and was previously found to be sensitive to dissociative effects of psychedelics and drugs of abuse, such as ketamine and THC (46–48).

Bowdle Visual Analog Scales

Psychedelic symptoms are assessed using a 13-item VAS (49). Two scales measure subjective "*high*" and "*drowsiness.*" From the other scales, composite scores of "*internal perception*" (reflecting inner feelings that do not correspond with reality) and "*external perception*" (reflecting a misperception of an external stimulus or a change in the awareness of the subject's surroundings) are calculated (50).

Profile of Moods States

The POMS is a self-assessment mood questionnaire with 72 items, rated on a 5-point Likert scale, with 0 being "not at all" to 4 "extremely." Participants have to indicate to what extent these items were representative of their mood at that moment. Eight mood states are classified and quantified by calculating the sum score of associated items for each mood state, i.e., *anxiety*, *depression*, *anger*, *vigor*, *fatigue*, *confusion*, *friendliness*, and *elation*. Two composite scales are derived; *arousal* and *positive* mood (51).

Procedure

Participants for both studies were recruited *via* advertisements. Data collection in the THC study was part of a more extensive study that included fMRI scanning after the booster dose. Participants of both studies were only included if they had prior experience with cannabis. They were medically examined by a physician, who checked for general health and took blood and urine samples for standard chemistry and hematology. Both studies were approved by the standing Medical Ethics Committee of Maastricht University and were carried out in compliance with the revision of the Declaration of Helsinki applicable at that time (i.e., Seoul, 2008; Fortaleza, 2013) and the International Conference on Harmonization guidelines for Good Clinical Practice. A permit for obtaining, storing, and administering cannabis and JWH-018 was obtained from the Dutch drug enforcement administration. All participants gave written informed consent and received financial compensation for their participation. All tests were taken after acute administration of the drug (see **Figure 1**).

Statistical Analyses

A student's *t*-test was used to compare differences in monthly cannabis use, while chi-square test was used to compare distributions of sexes between the two studies.

Outcome data that was normally distributed was analyzed using GLM Repeated Measures ANOVA, with Drug (placebo and drug condition (i.e., THC or JWH-018) as within-subject factor and Study (THC and JWH-018 study) as between-subject factor. Partial eta squared (partial η^2) is reported to demonstrate the effect's magnitude and is based on Cohen's f, which defines small, medium, and large effect sizes as, respectively 0.10, 0.25, and 0.40, which corresponds to partial η^2 values of 0.01, 0.06, and 0.14 (52). Subsequently, difference scores (THC/JWH-018 minus placebo) were analyzed with pairwise comparisons with a *t*-test for independent samples.

Non-normal distributed data was analyzed with the non-parametric Wilcoxon signed-rank test, to test for significant differences between the drug condition (THC or JWH-018) and placebo. Difference scores (THC or JWH-018–placebo) were tested with a Mann-Whitney test, to assess for differences between THC and JWH-018. A p-value of <0.05 was considered statistically significant. The effect size (r) for non-parametric tests is calculated by dividing the Z-score by the square root of N, indicating a large effect size using Cohen's d criteria of 0.10, 0.30, and 0.50 for defining small, medium, and large effect sizes. All statistical tests were conducted using IBM SPSS statistics, version 26.

Missing Data

There were several missing data due to technical malfunctioning or the participant not being capable of performing the test. For the THC study, CTT data from one participant in the THC condition was missing, as was DAT data from three participants in the placebo and three other participants in the THC condition. In the JWH-018 study, the following was missing: CTT-score for one participant in the JWH-018 condition; DAT for one

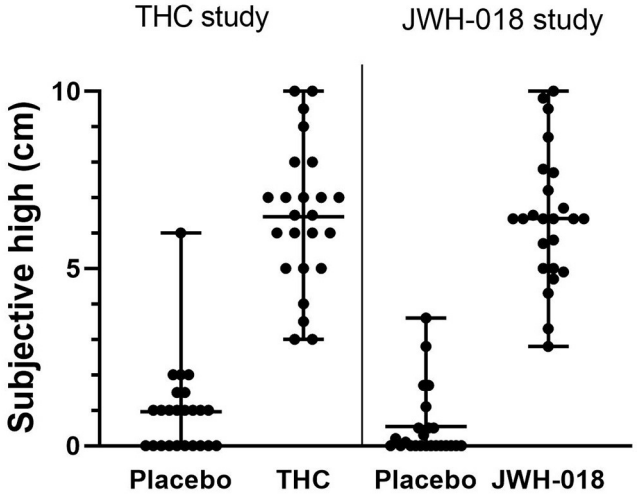

FIGURE 2 | Scatter plot with mean and range of subjective high scores in placebo and drug conditions in both samples.

participant in the placebo and one participant in the JWH-018 condition; SST data for one participant in the JWH-018 condition, and MFFT data for one participant in the placebo and one participant in the JWH-018 condition. Missing data of these participants were replaced by the study and condition's average before entering the RM ANOVA analysis.

RESULTS

Demographics

Participants in both groups used cannabis <10 times/month, nevertheless, the average consumption in the groups was statistically different [$t_{(46)} = 3.17$, $p < 0.01$]. Also, the division of sexes was significantly different according to a Chi-square test [$X^2(1, N = 48) = 8.89, p < 0.01$].

Subjective High

Individual subjective high scores per treatment condition are presented in **Figure 2**. Mean subjective high score was 6.46 after THC and 6.41 after JWH-018 administration. *Subjective high* score demonstrated a significant effect of Drug [$F_{(1, 46)} = 329.1$; $p < 0.001$, $\eta_p^2 = 0.88$]. No significant effect of Study or Drug x Study was found, confirming that subjective high in both samples was comparable.

Cognitive and Psychomotor Tests

Critical Tracking Task

GLM Repeated measures ANOVA showed a significant effect of Drug and Study on *CTT score* [$F_{(1, 46)} = 9.8$; $p = 0.003$, $\eta_p^2 = 0.18$; $F_{(1, 46)} = 8.88$; $p = 0.005$, $\eta_p^2 = 0.16$], indicating that drug conditions impaired performance (**Figure 3A**), as compared to placebo. Subsequent *t*-test analysis on the difference scores showed no significant difference between the change in CTT scores caused by THC or JWH-018 (**Figure 3B**).

Divided Attention Task

GLM Repeated measures ANOVA showed a significant effect of Drug on *tracking error* [$F_{(1, 46)} = 17.66$; $p < 0.01$, $\eta_p^2 = 0.27$] and *RT* [$F_{(1, 46)} = 5.25$; $p = 0.027$, $\eta_p^2 = 0.10$]. *Tracking error* and *RT* increased after the drug conditions (**Figure 3A**). *T*-test analysis showed that the change in tracking error and RT did not differ significantly between THC and JWH-018 (**Figure 3B**).

Control losses and *false alarms* were analyzed with the non-parametric Wilcoxon signed-rank test, which showed that these were significantly higher after drug conditions compared to the placebo conditions ($Z = -4.83$; $p < 0.01$; $r = 0.49$ and $Z = -4.14$; $p < 0.01$; $r = -0.42$). The change in number of control losses and false alarms was not different between THC and JWH-018, according to Mann-Whitney tests.

Stop Signal Task

Non-parametric testing showed that the number of *omission and commission errors* increased ($Z = -2.50$; $p = 0.012$; $r = -0.25$ and $Z = -2.68$; p=0.007; $r = -0.27$) in the drug conditions compared to placebo (**Figure 4A**). No effect was found on Stop or Go reaction time. Paired comparison of change scores from placebo demonstrated that the changes in number of omission and commission errors did not differ significantly between THC and JWH-018 (**Figure 4B**).

Matching Familiar Figures Test

GLM Repeated measures ANOVA demonstrated a significant effect of Study on *Latency* ($F_{(1, 46)} = 9.27$; $p = 0.004$) with participants in the JWH-018 study showing slower responses. GLM did not show an effect on *I-score*.

Non-normally distributed *E-score* and *errors* were analyzed using Wilcoxon signed-rank test, and this showed that the *E-score* significantly decreased after the drug conditions compared to placebo ($Z = -2.17$; $p = 0.03$; $r = -0.22$) (**Figure 4A**). No significant difference was found in the number of errors. Pairwise comparison of change scores from placebo indicated no significant difference on E-scores between THC and JWH-018 (**Figure 4B**).

Subjective Questionnaires

POMS

All scales of the POMS were analyzed using non-parametric testing. Wilcoxon signed-rank test showed that all scales of the POMS, except anger, were significantly different in the drug conditions compared to placebo (see **Supplementary Material** for *Z* and *p*-values). While scores on the *anxiety, depression, fatigue, confusion* scale increased, scores on *vigor, friendliness, elation, arousal, and positive mood* decreased after treatment (**Figure 5A**).

Pairwise comparison showed that scores on *vigor, friendliness, elation, and positive mood* were significantly different between THC and JWH-018 (see **Supplementary Material** for *U* and *p*-values) (**Figure 5B**).

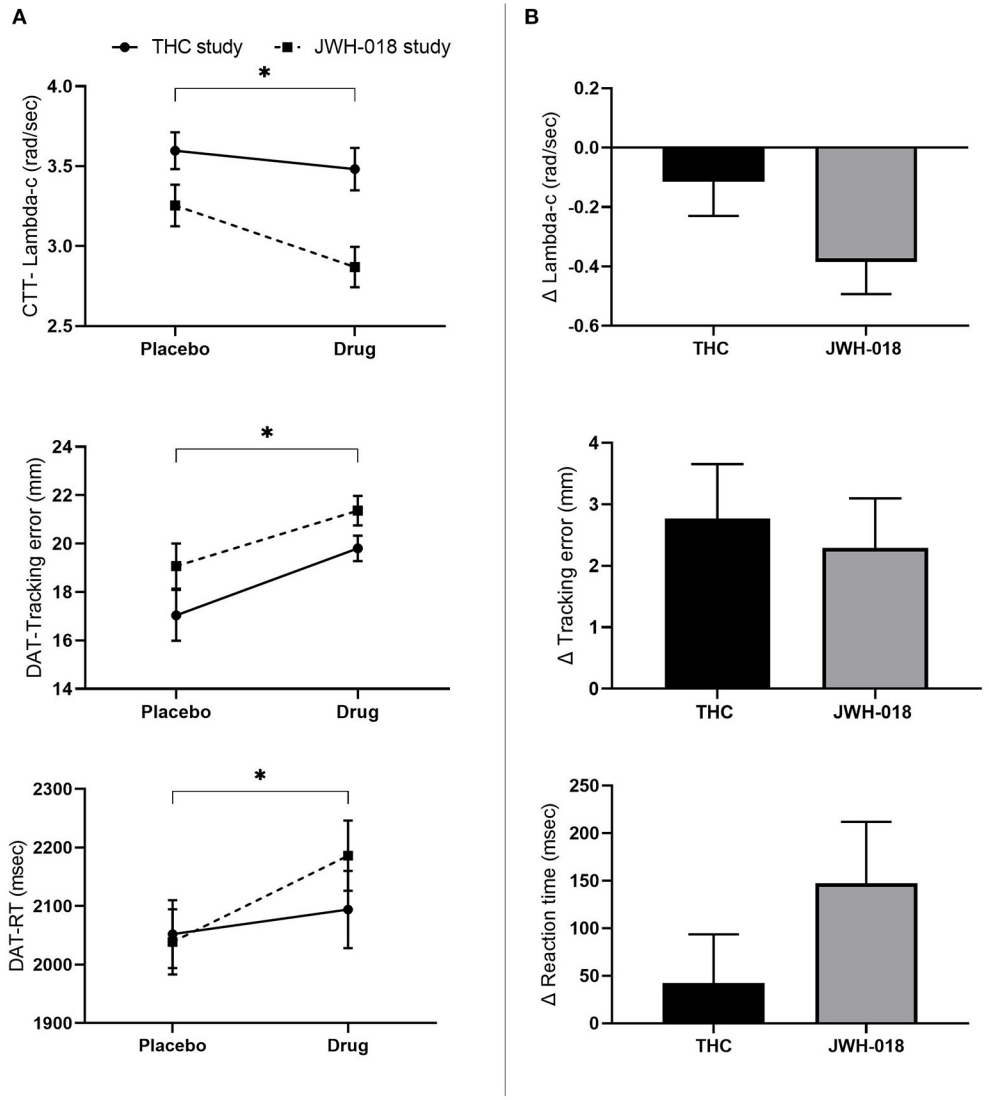

FIGURE 3 | (A) Mean (SEM) values for lambda-c in the critical tracking task, and tracking error and reaction time in the divided attention task for placebo and drug conditions, in the THC and JWH-018 study. **(B)** Lambda-c in the critical tracking task, and Tracking error and reaction time in the divided attention task for both drug conditions shown as difference scores (relative to placebo). *Significant difference between the active condition (THC/JWH-018) and placebo.

CADSS

All scales of the CADSS were analyzed non-parametrically, and responses were significantly higher in the drug conditions than in placebo (see **Supplementary Material** for *Z* and *p*-values) (**Figure 6A**). Pairwise comparison of change scores from placebo demonstrated that the scores in the JWH-018 condition were significantly higher than in the THC condition (see **Supplementary Material** for *U* and *p*-values) (**Figure 6B**).

Bowdle

Wilcoxon signed-rank tests showed that all scales of the Bowdle were significantly increased after drug treatment compared to placebo (see **Supplementary Material** for *Z* and *p*-values). Pairwise comparison of change scores from placebo showed that there was no difference in the scores on the Bowdle scales between THC and JWH-018.

DISCUSSION

Although SCs act on the same receptors as THC, it is not straightforward to compare these compounds based on equipotent doses due to the additional differences in affinity, and efficacy. Instead, in this study, the effects of an SC were compared with cannabis (THC), based on psychotropic dose equivalence as represented by subjective intoxication levels. We selected a group of occasional cannabis users who took part in a large THC study and, based on their acute subjective intoxication score,

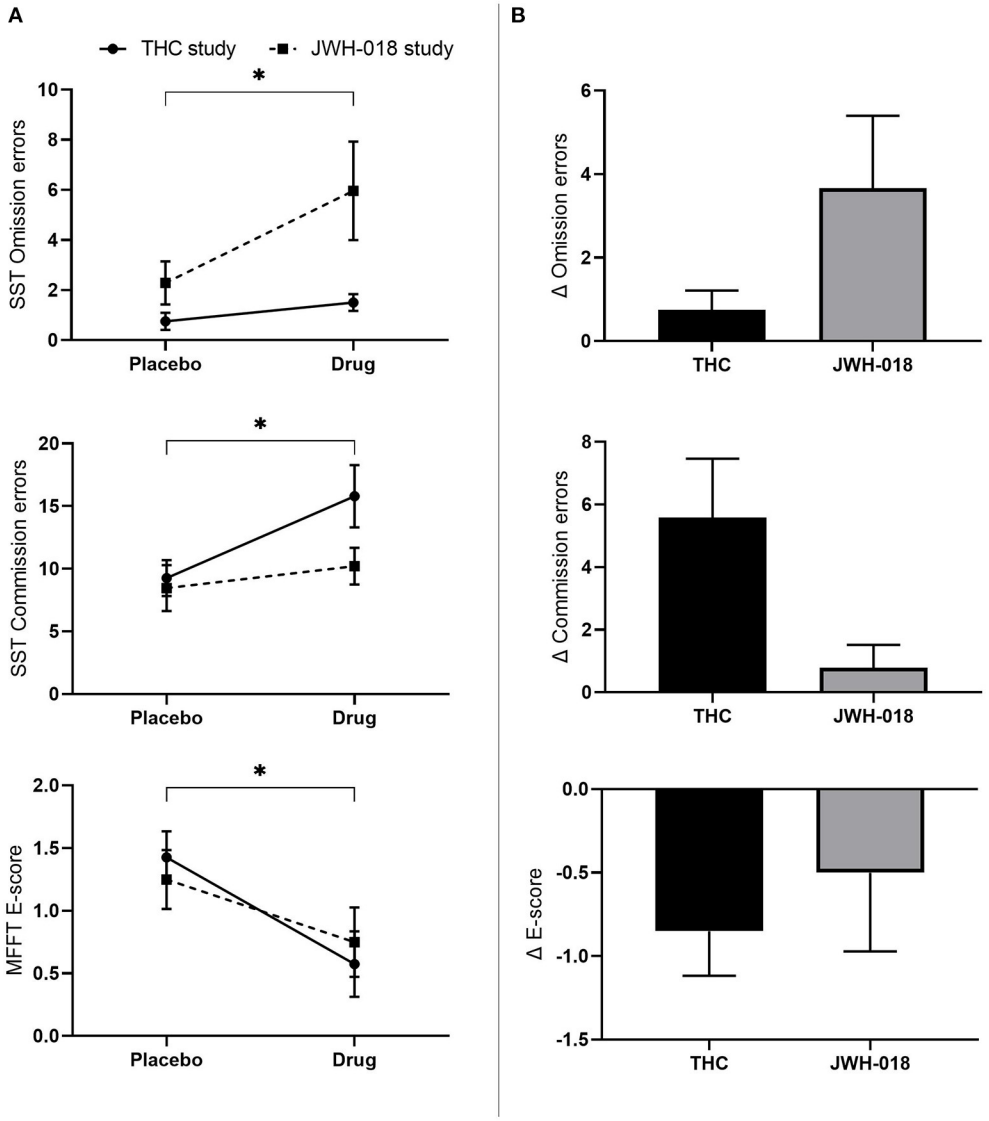

FIGURE 4 | (A) Mean (SEM) number of omission and commission errors in the stop signal task and E-score in the matching familiar figures test for placebo and drug conditions, in the THC and JWH-018 study. *Significant difference between the active condition (THC/JWH-018) and placebo. **(B)** E-score in the matching familiar figures test for both drug conditions shown as difference scores (relative to placebo).

matched these to a group of participants who took part in a JWH-018 study. The design and measures used in both studies were similar, making these datasets ideal for conducting this comparative analysis.

When using equipotent doses in our earlier study [i.e., with JWH-018 being 4–5 times as potent as THC, a dose 5 times as low as a standard THC dose was selected for JWH-018 (i.e., 3 mg JWH-018)], levels of subjective intoxication produced by JWH-018 were much lower than what has been shown previously for typical THC doses (29). In the current study, using psychotropic dose equivalence, i.e., at similar levels of subjective intoxication after both cannabinoids (i.e., 6.46 and 6.41 cm), comparable effects were demonstrated on cognitive performance tests. Both drugs impaired performance on psychomotor, divided attention, and impulsivity tasks with similar magnitudes. Likewise, no significant differences between THC and JWH-018-induced levels of cognitive impairment were found. Subjective questionnaires demonstrated that both drugs caused significant psychotomimetic effects but that the dissociative effects were considerably stronger for JWH-018 than for THC, while positive mood states were more affected by THC. Psychotomimetic effects of JWH-018 at psychotropic dose equivalence in the present study were higher than those observed at equipotent dose equivalence in a previous study (30), which underscores the relevance of distinguishing between these comparative approaches.

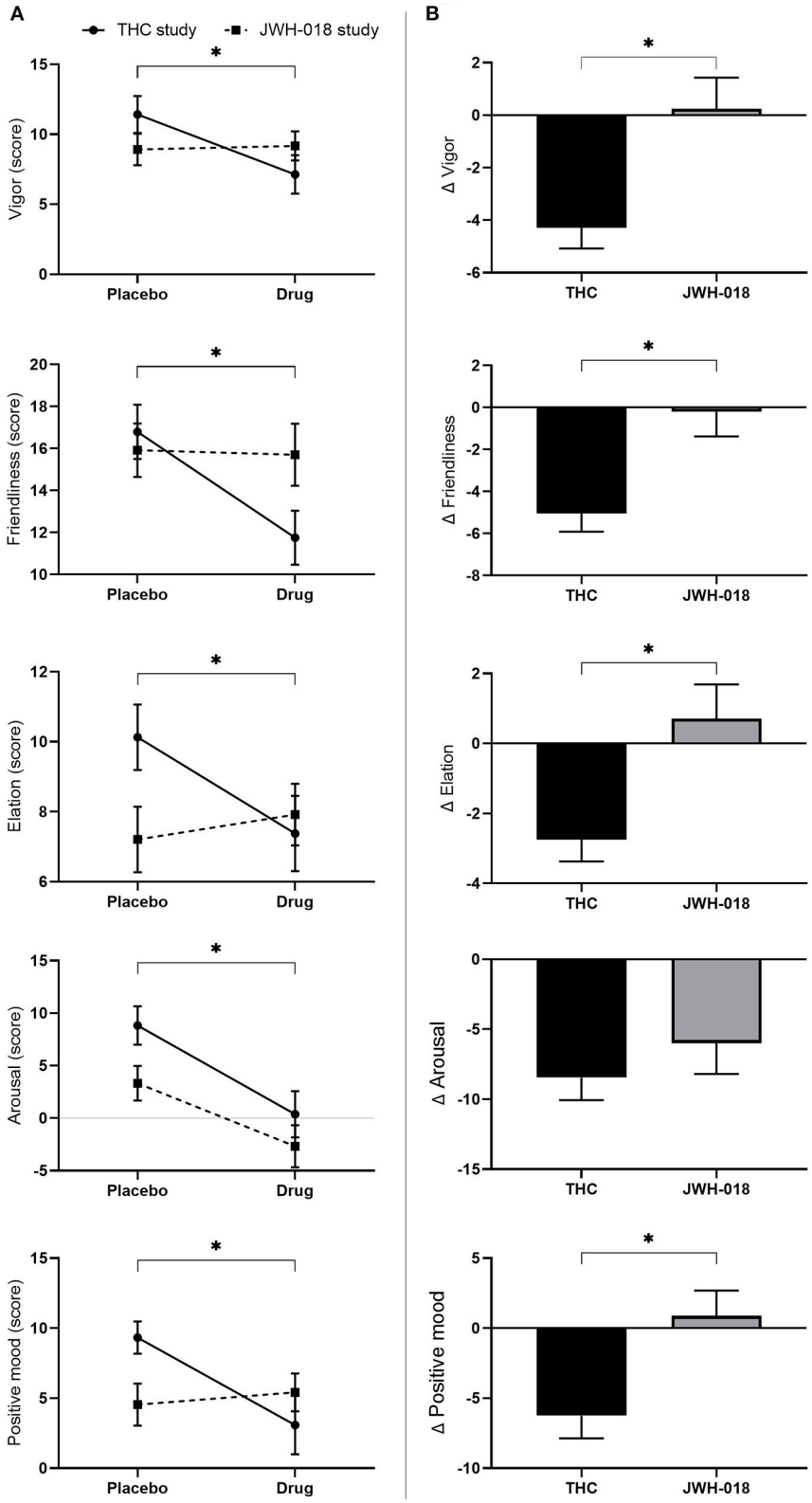

FIGURE 5 | (A) Mean (SEM) scores on the POMS scales vigor, friendliness, elation, arousal, and positive mood, for placebo and drug conditions, in the THC and JWH-018 study. *Significant difference between the active condition (THC/JWH-018) and placebo. **(B)** Scores on the POMS scales vigor, friendliness, elation, arousal, and positive mood for both drug conditions shown as difference scores (relative to placebo). *Significant differences between THC and JWH-018.

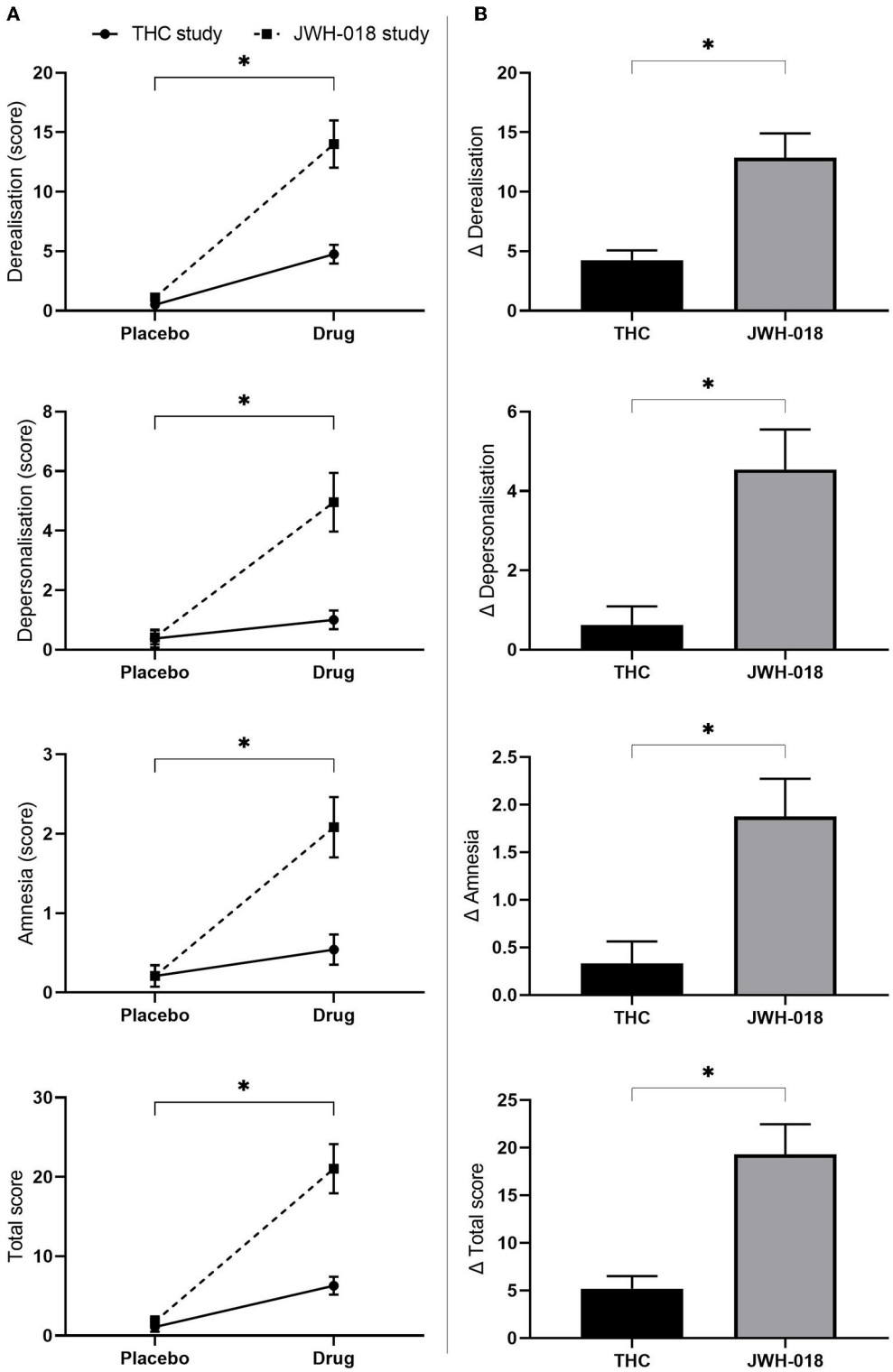

FIGURE 6 | (A) Mean (SEM) scores on the CADSS derealisation, depersonalisation amnesia, and total score for placebo and drug conditions, in the THC and JWH-018 study. *Significant difference between the drug condition (THC or JWH-018) and placebo. **(B)** scores on the CADSS derealisation, depersonalisation amnesia, and total score for both drug conditions shown as difference scores (relative to placebo); significant differences between THC and JWH-018.

Dissociative symptoms, known to occur in psychiatric disorders such as schizophrenia, have been reported during cannabis intoxication (53), and the link between the use of cannabis and psychosis has been reported recurrently (54–58). The risk of an adverse psychotomimetic experience after cannabis use is dose-related, with higher doses increasing the risk (59–61). The current finding that synthetic cannabinoids induce stronger psychotomimetic effects is in line with the many case reports and epidemiological data showing SCs to elicit psychotomimetic effects in vulnerable populations or patients with schizophrenia and healthy individuals (19, 55, 56, 62–64). The lack of cannabidiol (CBD), the non-psychoactive constituent of cannabis, might explain the increased risk of experiencing psychotomimetic effects after SC use. CBD, which is present in different ratios in natural cannabis, has been found to protect against THC's psychotic effect (65–69). It has also been suggested that, due to the higher efficacy, SCs alter the function of the neurotransmitter systems involved in schizophrenia, such as dopamine and glutamate, to a considerable extent (70). In addition, SCs yield metabolites with partial to full agonist activity (24), which again can interact with these neurotransmitter systems, leading to an increased effect. For THC, acute administration has been found to increase glutamate and dopamine levels (71), and increases in striatal glutamate levels were found to underlie the acute psychotomimetic effects of intravenously administered THC (72). It can be hypothesized that the association between striatal glutamate and psychotomimetic symptoms is even more prominent for SC due to their higher levels of efficacy. Studies into the effect of SCs on the neurotransmitter systems involved in schizophrenia are needed to determine the role of these systems in explaining the strong psychotomimetic effects compared to natural cannabis.

As in our previous studies (32, 34), the current analysis demonstrated that drug treatment (THC and JWH-018) affected mood states, with the negative states (except anger) increasing and the positive states decreasing. The decrease in friendliness, vigor, elation, and positive mood was apparent after THC, while both drugs decreased arousal. The effects of THC on mood have not been consistent in previous studies. Some studies showed no effect of THC on mood (73–75), while others demonstrated negative effects (76–78), whereas a more recent study showed elevated scores on positive states (79, 80). These inconsistencies in the effect of THC on mood can possibly be explained by essential differences in study designs, such as differences in dose, route of administration, time of assessment after dosing, and participants' drug use history. SCs users also often report negative mood changes (81) when intoxicated. This negative effect on mood was confirmed for JWH-018 in the current comparative analysis and in the previous studies (30, 32). However, in the current study, the changes in mood after JWH-018 appeared to be less prominent than after THC. This could be due to baseline differences in mood states, which were incorporated in the previous JWH-018 study (30, 32). However, no baseline measurement of mood was taken in the THC-study, hence no correction for baseline differences could be applied in the current study.

Participants in the current study were matched on subjective intoxication levels to accomplish psychotropic dose equivalence. However, there were significant differences in the average monthly consumption of cannabis and the males/females ratio in the two groups (83.3% males in the THC study vs. 41.7% in the JWH-018 study). With respect to cannabis use history, an earlier study comparing a large sample of infrequent and daily cannabis users demonstrated that the acute effects on neurocognitive performance were similar across users irrespective of their cannabis use history (33). With the current participants' use history falling in a much narrower range of cannabis use (i.e., excluding using more than 3 times/week), it is unlikely that this small difference in cannabis use history might have contributed to different findings for THC and JWH-018. With regard to sexes, there have been suggestions that women are more sensitive to the effects of THC than men (82). However, several studies were unable to confirm this, showing no differences between men and women in the acute effect of THC on neurocognitive function (80, 83). In the current study, it is also unlikely that sex differences significantly affected the study results. Men were overly represented in the THC study, but nevertheless, the effects of THC were apparent on a wide range of measures. Overall, by using the subjective high scores as the matching factor between our groups, potential confounding of differences in sex and cannabis use history between participants of the two studies were eliminated.

The proposed method of comparing drugs at psychotropic dose equivalence can also be applied to other drugs of abuse. Especially with the large number of NPS entering the market since the early 2000s, it has been challenging to determine the risks associated with these new compounds. The EMCDDA (84) has, nevertheless, recommended that individual health risks of NPS be assessed in pharmacological studies in humans and include psychological and behavioral measures. Moreover, the EMCDDA guidelines advise evaluating the risk of novel NPS relative to traditional drugs of abuse. However, when comparing different compounds within various drug classes, different neurotransmitter binding profiles are typical. Psychedelic drugs, for example, all act as agonists at the serotonin 2a receptor. Nonetheless, there is a wide variety in the subjective effects they can elicit (85), which is attributed to, among others, the binding affinities for serotonin receptor subtypes. Stimulants, on the other hand, typically act on multiple neurotransmitter systems, such as dopamine, noradrenaline, and serotonin (86, 87). However, based on their binding profiles, it is difficult to predict and compare effects (88). Therefore, to make a fair judgment on the neurocognitive and psychotomimetic effects and addictive potential of different drugs, it is advised to compare them based on psychotropic dose equivalence. When using psychotropic dose equivalence in other drug classes, it is advised to use the primary subjective motive for that class of drugs, e.g., feeling energetic with stimulants, or experiencing broadened consciousness with psychedelics (89). In the current study, subjective intoxication levels were used to determine psychotropic dose equivalence, as feeling high is the primary goal for recreational users of cannabinoids.

Up until now, more than 190 SCs have been reported by the EMCDDA, and only for a few of them the acute effects have been studied in humans (29–32, 90, 91). In addition, the most recent generations of SCs, which show increased potency and efficacy at CB1 receptors (92, 93), have not yet been tested in controlled studies. Whether using equipotent dose or psychotropic dose equivalence, controlled clinical studies with SCs and other NPS are challenging for ethical and safety reasons. A safe starting dose should be determined using all available preclinical data on pharmacology, toxicology, pharmacokinetics, and pharmacodynamics, including information retrieved from recreational users. It is vital to find a balance between minimizing the risks and maximizing the benefits (i.e., eliciting a pharmacological response). Furthermore, first-in-human studies with NPS should be conducted as phase 1 studies and implement the guidelines and regulations associated with this type of research (94).

CONCLUSIONS

Findings in the present study suggest that the method of psychotropic dose equivalence is more accurate to predict drug outcome as compared to the method of dose equivalence (i.e., based on differences in potency). At psychotropic dose equivalence, THC and JWH-018 impaired cognitive performance to a similar extent, while dissociative effects were more pronounced for JWH-018 than for THC, and positive mood states were more affected by THC. The effects of JWH-018 that we reported in previous laboratory studies may have underestimated the neurocognitive and psychotomimetic effects that SC users may experience in real life when they achieve their maximal desired state of subjective high. In addition, with the high potency of SCs and the inconsistent content of smoking mixtures, it is very difficult for users to predict the maximal subjective high, resulting in very unpredictable neurocognitive outcomes and common overdosing.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medisch-Ethische Toetsingscommissie azM/UM. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ET: analysis of data and writing manuscript. JR, NM, and ET: interpretation of data. All authors: conceptualization and reviewing the manuscript. All authors approved the submitted version of the manuscript and agreed to be accountable for all aspects of the work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.891811/full#supplementary-material

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Efficiency of Inhaled Cannabidiol in Cannabis Use Disorder: The Pilot Study Cannavap

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Introduction: Cannabidiol (CBD), the second most prevalent cannabinoid found in cannabis, is considered to be safe for use. Studies suggest that CBD may be of benefit in treating cannabis use disorder (CUD). In clinical practice, CBD is already being used by patients who are trying to reduce or stop their cannabis consumption. The aim of this study was to assess the potential of CBD inhaled using a vaping device in CUD.

Methods: This was an exploratory, observational, non-randomized, open-label study conducted at an Addiction Support and Prevention Center in Paris. The primary endpoint was a reduction of at least 50% in the reported number of joints consumed daily at 12 weeks. The participants were given an electronic cigarette along with liquid containing CBD. Nicotine at 6 mg/ml could be added in case of co-consumption of tobacco. They were assessed once a week and the CBD liquid dose was adjusted based on withdrawal signs and cravings (33.3, 66.6 or 100 mg/mL).

Results: Between November 2020 and May 2021, 20 patients were included and 9 (45%) completed the follow-up. All of the participants used tobacco, and were provided a liquid with nicotine. At 12 weeks, 6 patients (30%) had reduced their daily cannabis consumption by at least 50%. The mean number of joints per day was 3, compared to 6.7 at baseline. The mean amount of CBD inhaled per day was 215.8 mg. No symptomatic treatment for cannabis withdrawal was prescribed. Mild adverse effects attributable to CBD and not requiring the prescription of any medicines were reported in a few patients.

Conclusion: This research provides evidence in favor of the use of CBD in CUD. It also highlights the benefits of inhalation as the route of CBD administration in patients who use cannabis: inhalation can allow users to self-titrate CBD based on their withdrawal symptoms and cravings. This study illustrates the interest of proposing an addictological intervention targeting at the same time tobacco and cannabis dependence in users who are co-consumers. A double-blind, randomized, placebo-controlled clinical trial is needed to assess the efficacy of inhaled CBD in CUD.

Study registration number (IDRCB) issued by the ANSM (*Agence nationale de sécurité du médicament et des produits de santé*—French National Agency for Medicines and Health Products Safety): 2018-A03256-49.

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INTRODUCTION

Cannabis is the most produced and consumed illicit substance in the world. In 2019, the UN estimated that 4% of people aged 15–64 had consumed cannabis and that there were 200 million cannabis users worldwide—an increase of 18% since 2010 (1). In France, 42% of adults have tried cannabis and 11% of people aged 18–64 years are regular users (2). Cannabis smoking leads to increased cough, phlegm, susceptibility to upper respiratory infections, acute psychiatric symptoms such as anxiety and panic and to cannabinoid hyperemesis syndrome in a subset of genetically susceptible people (3, 4). It also increases the risk of cancer and cardiovascular disease when consumed by combustion in association with tobacco. The vast majority of French cannabis users co-consume cannabis and tobacco in the form of joints (5). Most cannabis users therefore have a dual dependency to cannabis and tobacco.

There is currently no specific regulatory-approved treatment for cannabis use disorder (CUD) other than symptomatic treatments for withdrawal symptoms (such as anxiolytics and hypnotics) (6). When chronic users stop using cannabis or reduce their consumption, this can lead to a withdrawal syndrome defined in the DSM-5 as the appearance of three or more of the following symptoms: irritability, anger or aggression; sleep difficulty; decreased appetite or weight loss; restlessness; depressed mood; other physical symptoms such as abdominal pain, tremors, sweating, fever, chills and headaches (7). These symptoms most commonly occur within 24–48 h of withdrawal and can last for up to 4 weeks after cessation of use (6). The Cannabis Withdrawal Scale (CWS) has been validated in English and comprises two subscores ranging from 0 to 190 representing the intensity of withdrawal symptoms and the impact of these symptoms on daily life (8). There are currently no validated scales in French designed to assess withdrawal symptoms or cannabis craving intensity. In clinical practice, visual analog scales (VAS) ranging from 0 to 10 are sometimes used.

Cannabidiol (CBD) is the second most prevalent cannabinoid in cannabis, after Δ-9-tetrahydrocannabinol (THC) (9). Unlike THC, CBD has no hedonic effects (10). Based on the current understanding of CBD, it appears to be a modulator of the endocannabinoid system [a weak antagonist of CB1; (11)], a serotonin receptor agonist *via* the 5-HT1a receptors (12–14) and an allosteric modulator of the μ and δ opioid receptors (15). It may also have an impact on the glutamatergic system (12). Its therapeutic properties are still being studied. It is an anticonvulsant used in particular for certain resistant forms of childhood epilepsy [Dravet syndrome and Lennox Gastaut syndrome; (16, 17)]. Certain studies have identified possible neuroprotective, analgesic, anti-inflammatory, anti-emetic and even anti-cancer effects (18, 19).

The bioavailability of orally administered CBD is 6%, compared to 31% for inhaled CBD (18, 20–22). Peak plasma concentrations are reached 3–10 min after inhalation and are higher than those obtained after ingestion. This route of administration has the advantage of limiting the first pass effect. After inhalation, the elimination half-life is long- −31 h on average (+/−4 h)—and can vary depending on different parameters, such as differences in metabolism, distribution, accumulation in adipose tissue, and biliary and renal excretion (20).

To date, CBD appears to carry a very low risk of toxicity (23–25). The main reported side effects at high doses in studies evaluating CBD in epilepsy were diarrhea, sedation, nausea, headache and changes to appetite. Abnormal liver function tests and pneumonia have also been reported in certain epilepsy studies, but may have been caused by co-administration with anti-epileptic drugs. In a recent metaanalysis, after excluding studies in childhood epilepsy, the only adverse outcome associated with CBD treatment was diarrhea (26). A phase I study involving CBD administration in healthy subjects did not identify any concerning short-term physical or mental effects for CBD doses of up to 6,000 mg daily (27). Furthermore, there is no reported evidence of addictive potential in animal models or humans, and there are no reported cases of CBD misuse.

Numerous psychiatric studies have been conducted into the effects of CBD. CBD appears to have an anxiolytic effect (reduced anxiety with single oral doses of 300–600 mg) (28–31) and an anti-psychotic effect (oral doses of 150–1,500 mg per day) (9, 32). There is scientific justification for a possible anti-depressant effect (9, 12).

From a neurobiological perspective, CBD acts on the endocannabinoid systems involved in the reward pathway *via* the CB1 receptors (11, 33), which suggests that cannabinoids may have therapeutic potential in substance use disorders, regardless of the substance. A potential therapeutic effect of CBD in substance use disorders (opiates, alcohol, smoking, amphetamines, cannabis etc.) can be considered on the basis of preclinical (34, 35) and clinical studies: a reduction in cravings and anxiety was found in former opiate users (36), while the daily number of cigarettes smoked went down when CBD was vaped at a dose of 400 μg (37). However, despite encouraging preclinical and observational data (38), two randomized, placebo-controlled trials did not find any benefits of CBD in cocaine use disorder (39, 40). Several clinical trials have suggested that nabiximols (a sublingual spray containing THC/CBD extracts in a 1:1 ratio) may reduce the intensity of cannabis withdrawal signs (41, 42) and reduce cannabis use both during treatment (43) and for an extended period after treatment cessation (44). Given that studies of dronabinol (THC only) demonstrated its efficacy in reducing withdrawal symptoms but found no effect on abstinence or reduced consumption compared to placebo (45), the reduction

in consumption observed with nabiximols may be attributable to the CBD it contains.

To date, only three studies have been published assessing the use of CBD in cannabis use disorder. Two case reports suggest a reduction in cannabis withdrawal symptoms, one with daily oral administration of 400–600 mg CBD tablets (53) and the other with 18–24 mg oral CBD in oil form (46). A phase IIa, randomized, double-blind, placebo-controlled clinical trial was conducted to identify the most effective oral dose of CBD in terms of increased number of days of abstinence from cannabis and lower urinary THC metabolite levels (THC-COOH:creatinine ratio) (47). CBD doses of 400 and 800 mg appeared to be more effective than CBD 200 mg or placebo at reducing cannabis consumption. In addition, CBD appeared to reduce the number of cigarettes smoked and signs of cannabis withdrawal. No differences were found between CBD and placebo in terms of side effects.

The use of electronic cigarettes has been shown to be effective in reducing cigarette consumption and in smoking withdrawal, with a better risk-benefit ratio for vaping (48, 49). In France, the production, sale and use of e-liquids containing CBD is currently legal provided the liquid contains <0.3% THC and the CBD comes from the fiber or seeds of hemp varieties authorized for industrial and commercial use (50). CBD e-liquids are treated as standard consumer goods. In clinical practice, CBD is already being used by patients who are trying to self medicate to reduce their cannabis consumption or stop using cannabis entirely (51).

The use of CBD by inhalation rather than taken orally is particularly interesting given its better pharmacokinetic properties (faster peak plasma levels and better bioavailability). Moreover, the advantage of the electronic cigarette is that it could allow users to self-titrate CBD in the same way that it is used to self-titrate nicotine (52), which would enable each user to adjust their consumption based on their needs and the effects experienced. In a context of limited scientific data on the dosage of CBD that could be effective in CUD, the use of a device allowing self-titration permits to explore the therapeutic potential of this product without being limited by the constraint of fixed doses imposed by the galenic of the tablet. Finally, vape allows for clinical addictological work on the behavioral component of smoked cannabis consumption, which is not possible with CBD tablets or oil.

In the absence of any standard treatment for cannabis withdrawal and given the possibility that CBD may help reduce cannabis consumption in users, it seems pertinent to consider the role CBD vaping might play in the reduction and cessation of cannabis use. No studies have assessed this to date. The aim of this study was therefore to conduct a pilot study to assess the benefits of CBD inhaled *via* an electronic cigarette in reducing or stopping cannabis use.

MATERIALS AND METHODS

We conducted an interventional, single-center, non-randomized, uncontrolled, open-label study. It took place at a community addiction facility that offers free, anonymous support on an outpatient basis: the CSAPA (*Center de Soins d'Accompagnement et de Prévention des Addictions*–Addiction Support and Prevention Center) located at 110 les Halles, Paris.

Endpoints

The primary endpoint was a reduction of at least 50% in reported cannabis consumption, measured in terms of number of joints per day after 12 weeks, compared to reported consumption at baseline.

The secondary endpoints were: daily amount of inhaled CBD, total amount spent on cannabis daily (in euro), cannabis cravings visual analog scale (VAS) score from 0 to 10, withdrawal symptom intensity VAS score, the two CWS subscores, number of cigarettes smoked per day, exhaled carbon monoxide level measured using an electronic device, occurrence of adverse effects and prescription of symptomatic treatments for signs of cannabis withdrawal.

Participants

To participate in the study, the patients had to be adults with cannabis use disorder (based on the DSM-5 substance abuse disorder criteria), have health insurance/social security coverage, have contacted the CSAPA at 110 les Halles, Paris in the hope of reducing or stopping their cannabis use, and test positive for THC in a urine toxicology test at the first medical consultation.

The exclusion criteria were the presence of any acute psychopathology, legal guardianship, a use disorder for any substance other than cannabis (except cigarettes) and pregnancy and/or breastfeeding. Participation in the study was free, anonymous and at no financial cost to the participant.

The number of subjects to include was arbitrarily set at 20, given the modest human and financial resources at our disposal for the study.

Follow Up Process

Patients interested in participating in the study met with one of the study doctors, who provided them with clear, comprehensive information. The inclusion and exclusion criteria were also checked during this meeting. The patients were given a written information sheet. After a reflection period of at least 48 h, they came in for a baseline visit, during which they signed a consent form.

The follow-up lasted 12 weeks in total (**Figure 1**). The participants attended eight medical visits, the first four at 1 week intervals and the rest every 2 weeks. The following were assessed at each visit: daily joint consumption, total amount spent on cannabis in euros, signs of cannabis withdrawal (irritability, anger, sleep difficulty, decreased appetite or weight loss, restlessness, depressed mood; abdominal pain, tremors, sweating, fever, chills and/or headaches), side effects attributable to CBD, number of cigarettes smoked per day and exhaled carbon monoxide. Symptomatic treatment for signs of cannabis withdrawal and nicotine replacement therapy could be prescribed for the duration of the study.

After the first medical visit, the patients had a consultation with a nurse to teach them how to use the electronic cigarette. At the end of this consultation, they were given a 30-mL bottle

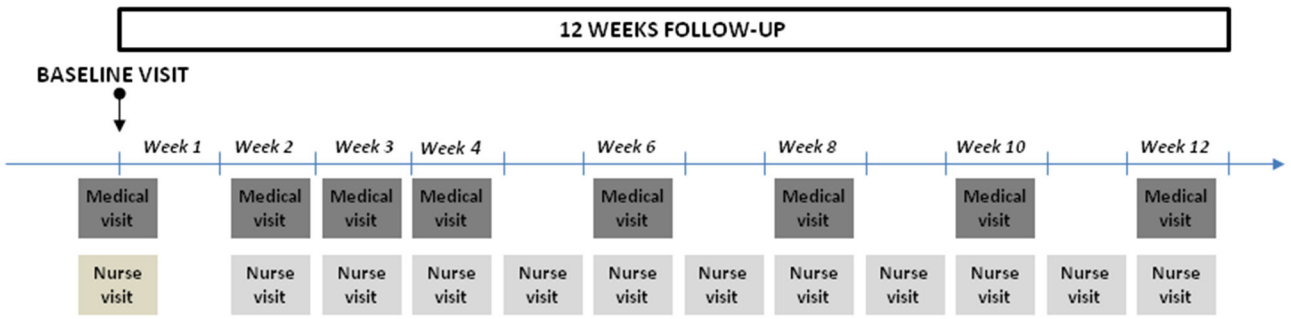

FIGURE 1 | Timeline of the follow-up.

of liquid containing 33.3 mg/mL CBD, with or without nicotine at 6 mg/mL, with a flavor of their choice (tobacco, red berries or cannabis). Obtaining a liquid with nicotine was recommended in case of tobacco consumption to limit the risk of increased cigarette consumption or signs of tobacco withdrawal, but left to the choice of the participants. The liquids were purchased from the compagny Leaf, which produced them specifically for the study. The starting CBD dose of 33.3 mg/mL was selected based on clinical trials of CBD in anxiety, which identified an anxiolytic effect of CBD at oral doses of 300 mg and over. The administered CBD dose was reassessed every seven days (at the pharmacodynamic steady state, i.e., after five CBD half-lives). At this point, one of the study nurses also interviewed the patients to assess daily CBD consumption, the number of joints smoked per day, cannabis cravings VAS score, withdrawal signs VAS score and CWS score. The use of the vaping device was also assessed regularly, new coils could be provided and patients were reminded how to use the electronic cigarette, where necessary. The CBD liquid dose was adjusted depending on these data: it could be increased to the higher dose (if the cannabis cravings VAS score was $\geq$ 5/10 and/or the withdrawal signs VAS score was $\geq$ 5/10), reduced to the lower dose (cannabis cravings $\leq$ 2/10 and withdrawal signs $\leq$ 2/10) or continued at the same dose in the other possible scenarios. We settled for these cut-off values because they seemed to us clinically relevant. Three different concentrations of CBD were available, with nicotine or without nicotine at a single dose of 6 mg/mL: 33.3 mg CBD per mL, 66.6 mg CBD per mL, and 100 mg CBD per mL. The participants could visit the CSAPA between the follow-up nurse visits if they had any problems using the electronic cigarette of if they needed to collect more CBD liquid at the same concentration.

Statistical Analysis

Analyses were performed using an observed method. Because of the small cohorts, we report no inferential statistical analyses; outcomes are summarized by descriptive statistics. All analyses were performed using R Studio 4.0.0® or higher.

For the primary endpoint, descriptive statistics were performed for the last visit across all doses of CBD. Those lost to follow up were deemed not to have met the primary endpoint

For secondary endpoints, descriptive analysis was conducted, using a Chi-square or Fisher test, to identify factors impacting on the primary endpoint. The missing data were not imputed for secondary endpoints.

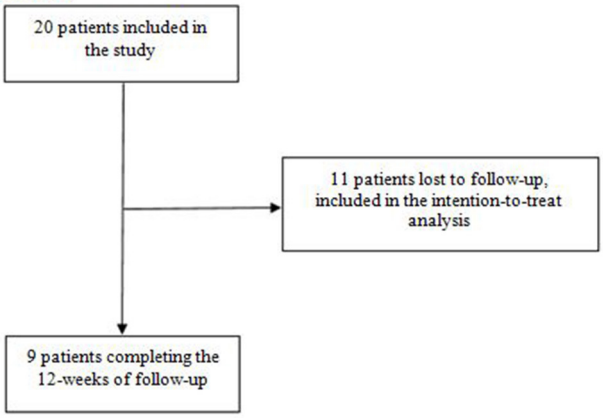

FIGURE 2 | Flow chart.

RESULTS

The study took place from 10/09/2020 to 05/12/2021. Twenty patients were included, and nine participants (45%) completed the full 12 weeks of follow-up (**Figure 2**).

Sample Characteristics

The patients were mostly men (90%), young (mean age 36 years, youngest 21 years and oldest 61 years), single (80%) and in employment (65%) (**Table 1**). The majority of the patients had a history of psychiatric illness (65%): either a mood or anxiety disorder. Fifty percent of the patients had a history of a use disorder for a substance other than cannabis or cigarettes. Eighty percent of the patients were smokers, most of them had already tried a vaping device (75%) and half had previously tried CBD. All the patients consumed cannabis solely in the form of joints containing both cannabis and tobacco, with the exception of one patient who smoked it using a water pipe (bong). The mean number of joints consumed per day was 6.7 (minimum

1.5, maximum 20). Two thirds of the patients were aiming for abstinence, while the other third wanted to control their use.

Primary Endpoints

At the end of the 12 weeks of follow-up, nine patients were still being followed up. Six patients (30% of the participants) had reduced their cannabis consumptions by at least 50% (**Table 2**), accounting for 67% of the 9 participants still being followed up at 12 weeks.

Secondary Endpoints

After 12 weeks of follow-up, the mean number of joints consumed per day was 3 (minimum = 0, maximum = 7), compared to a mean of 6.7 joints per day at baseline for all of the participants, and a mean of 5.44 joints per day at baseline for the 9 participants who ended up completing the follow-up. Three participants had stopped using cannabis entirely. The mean total amount spent on cannabis per day was €4.40, compared to €10.75 at baseline. The participants soon needed to increase the concentration of CBD in their liquid (**Table 3**). The mean amount of CBD inhaled per day was 215.8 mg at 12 weeks. No symptomatic treatment for cannabis withdrawal was prescribed, since only mild signs of withdrawal were observed during the medical follow-up.

No participants returned negative THC urine tests during the study.

With regards to smoking, all the patients chose fluid containing nicotine. Four (20%) received nicotine replacement therapy. The mean number of cigarettes smoked per day was 2.67 per participant at 12 weeks, compared to 7 at baseline. At 12 weeks, 2 of the patients who were smokers at baseline had stopped smoking cigarettes. The participants' exhaled carbon monoxide levels decreased compared to baseline: 50% of the patients (4) had a CO level below 10 ppm at 12 weeks compared to 26.3% at baseline (**Table 4**).

Mild adverse effects attributable to CBD and not requiring the prescription of any medicines were reported in 12 patients (60% of participants): irritation of the upper airways with or without cough in seven patients (35%), four of whom were lost to follow-up and three of whom reported that this symptom disappeared quickly during the follow-up period; temporary fatigue in 6 patients (30%); and self-limiting diarrhea in one patient (5%). At each visit throughout the follow-up period, the majority of patients presented with no adverse effects.

Subgroup Analysis

At 4 weeks, the six participants who reduced their daily joint consumption by at least 50% were consuming more CBD than the other participants: 221 mg/day compared to 66 mg/day (with mean consumption of 149 mg/day inhaled CBD for all the participants). There were no differences between these two groups at 8 weeks (190 mg/day on average) or at 12 weeks (215 mg/day on average).

TABLE 1 | Participant characteristics.

Characteristics	$N = 20^a$
Gender	
Male	18 (90%)
Female	2 (10%)
Age	36 (32,48)
Marital status	
Single	16 (80%)
Partnered	4 (20%)
Employment category	
Farmer	0
Tradesperson/retailer, small business owner	5 (25%)
Highly educated professionals and managers	8 (40%)
Middle managers, teachers and non-managerial health and social care professionals	0
Non-managerial employees	4 (20%)
Manual workers	3 (15%)
Retired - economically inactive	0
In employment	
No	7 (35%)
Yes	13 (65%)
Housing	
Home owner	3 (15%)
In rental accommodation	13 (65%)
In hostel	3 (15%)
Homeless	1 (5%)
Health insurance coverage	
CPAM [national health insurance] and private health insurance	10 (50%)
CPAM and no private health insurance	1 (5%)
CMU [universal health insurance] and private health insurance	1 (5%)
CMU and CSS [additional health insurance for people on a low income]	6 (30%)
AME [state medical aid for undocumented immigrants]	2 (10%)
Psychiatric comorbidity	
None	7 (35%)
Mood disorder	9 (45%)
Anxiety disorder	4 (20%)
Psychosis	0
Cigarette smokers	16 (80%)
Previous use of vaping device	16 (75%)
Previous use of CBD	10 (50%)
Cannabis use characteristics	
Age at first use	16 (12,21)
Age at loss of control	25 (18,30)
Product type/method of consumption	
Resin	6 (30%)
Cannabis buds	1 (5.0%)
Resin and buds	13 (65%)
Method of consumption	
Joint	19 (95%)
Vaporiser	0
Other	1 (5%)
Number of joints per day	6.7 (4.8, 8.5)
Total spent per day (€)	10.75 (0, 23)
Addiction objective	
Abstinence	13 (65%)
Controlled use	7 (35%)

[a] *n (%); mean (IQR).*

TABLE 2 | Change in primary endpoint 1.

	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12
≥50% reduction in daily joints[a]	6 (30%)	5 (25%)	8 (40%)	6 (30%)	5 (25%)	4 (20%)	6 (30%)
≤50% reduction in daily joints[a]	14 (70%)	15 (75%)	12 (60%)	14 (70%)	15 (75%)	16 (80%)	14 (70%)
Total number of patients still followed up	18	15	15	12	11	9	9
Lost to follow-up	2	5	5	8	9	11	11

[a]*n (%) 1.*

TABLE 3 | Change in CBD consumption during follow-up.

	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12
33.3 mg/mL liquid[a]	18 (100)	7 (47)	2 (13)	2 (17)	0	0	0
66.6 mg/mL liquid[a]	0	7 (47)	10 (67)	2 (17)	3 (27)	1 (11)	1 (11)
100 mg/mL liquid[a]	0	1 (6.7)	3 (20)	8 (67)	8 (73)	8 (89)	8 (89)
Total number of participants	18	15	15	12	11	9	9
Lost to follow-up	2	5	5	8	9	11	11
CBD consumed by participants (mg/day)[b]	56 (48)	123 (130)	149 (129)	190 (197)	190 (197)	235 (190)	216 (125)

[a]*n (%);* [b]*mean (standard deviation).*

TABLE 4 | Change in consumption between baseline and 12 weeks.

Characteristics	Baseline ($N = 20^a$)	12 weeks ($N = 20^a$)
Number of joints per day	6.70 (3.42)	3 (3)
Lost to follow-up		11
Total amount spent on cannabis per day (€)	10.8 (5.8)	4.2 (4.8)
Lost to follow-up		11
Daily concentration of inhaled CBD (mg/day)	56 (48)	216 (125)
Lost to follow-up		11
Carbon monoxide level		
0 to 4 ppm	4 (21%)	2 (25%)
5 to 9 ppm	1 (5,3%)	2 (25%)
10 to 14 ppm	5 (26%)	3 (38%)
15 to 24 ppm	5 (26%)	0 (0%)
> 24 ppm	4 (21%)	1 (12%)
Lost to follow-up		12
Number of cigarettes per day	7 (6)	2.67 (2.50)
Lost to follow-up		11

[a]*Mean (SD); n (%).*

At week 12, the patients who had reduced their cannabis consumption by at least 50% had a lower mean CWS withdrawal intensity score (19.83) than the group that had not reduced their consumption by 50% (62.33), with a mean overall score of 34 for all the participants who were still being followed up. They also had a lower mean CWS impact on daily life score (3.5) compared to the other group (8), with an overall mean of 5 for all the participants. The mean cannabis withdrawal symptoms VAS score was also lower in the subgroup that reached the primary endpoint: 0.83 compared to 6.33 in the other group, with an overall mean of 2.67.

DISCUSSION

This pilot study is the second clinical study to assess the benefits of CBD in cannabis use disorder (CUD). It is the first clinical study to explore the inhalation of CBD *via* a vaping device in a substance use disorder. At the end of the 12-week follow-up period, 6 users (30% of the participants) had managed to reduce their cannabis consumption by at least 50%. All participants chose the option of adding nicotine in the liquids. Although this is a pilot study involving a small number of participants, this research provides evidence in favor of the use of CBD in CUD. It also shows that people with CUD can use an electronic cigarette as a tool to reduce their cannabis consumption, and that it is possible to support them with this at an outpatient addiction center.

One of the aims of our study was to assess the amount of inhaled CBD required to reduce consumption. Since the bioavailability of inhaled CBD is 3–4 times higher than that of oral CBD, we used a liquid with a concentration of CBD that would enable users to vape around 100 mg CBD per day (i.e., 3 mL of liquid dosed at 33.3 mg/mL), which would seemingly correspond to an anxiolytic dose (26, 27, 29). The mean daily inhaled CBD consumption per patient was 215.8 mg, equivalent to 3.24 mL of liquid dosed at 66.6 mg/mL. After 4 weeks of follow-up, the group of participants who had reduced their cannabis consumption by at least 50% had a higher mean CBD consumption than the other participants (221 mg/day). This difference then disappeared, with the mean for both subgroups converging around 200 mg/day. It may therefore be worth

advising someone who wants to use CBD to reduce their cannabis consumption to use a liquid with a high concentration of CBD. Very few of our participants used the 33.3 mg/mL liquid after the start of the follow-up. If a larger scale study were to be conducted, we would suggest using liquids with a minimum concentration of 60 mg/mL. In April 2022 in France, a vial of 10 ml of liquid with a CBD concentration of 60 mg/ml cost between 18 and 30€, which corresponds to a price of 6 to 10€ for one person to inhale 200 mg of CBD per day. In practice, there is significant variability in the amount of CBD absorbed by each patient, depending on how they vape (amperage of the electronic cigarette coil, selected wattage, method of inhaling etc.). This limits the relevance of the "amount of CBD consumed per day" variable calculated simply as a function of the amount of liquid vaped per day and the concentration of CBD in the liquid. However, the interest of the inhalation by electronic cigarette is that each user can control the quantity of CBD absorbed according to the quantity of liquid consumed and its way of vaping by auto-titration (52).

The fact that no treatments were prescribed for cannabis withdrawal symptoms suggests that CBD is effective against these symptoms. The protocol did not specify when medicines for these symptoms should or should not be prescribed; this was left to the discretion of the two study doctors. It is also possible that the patients had few signs of withdrawal due to the gradual nature of the reduction in their consumption (or due to a lack of reduction, in some cases).

The patients who reached the primary endpoint at 12 weeks had less intense cannabis withdrawal symptoms, according to the VAS and CWS, and these symptoms had less of an impact on their daily life, as measured by the CWS. Our initial hypothesis is that these were "responder" patients, in whom CBD satisfactorily calmed withdrawal signs, either for reasons relating to interpersonal variation in response to this substance, or for reasons relating to interpersonal variability in withdrawal symptoms. It would appear likely, for example, that CBD would better soothe a patient whose main cannabis withdrawal symptom was anxiety than a patient whose main symptom was insomnia. A second hypothesis is that some of these participants had reduced their consumption at the start of the follow-up and were therefore distanced from any cannabis withdrawal symptoms that they may have experienced (since these symptoms last <1 month from withdrawal). Patients whose consumption fluctuated between reductions and increases would have cannabis withdrawal symptoms for longer than patients who managed to quickly reduce or stop their use.

The most common CBD adverse effect—irritation of the airways, reported by one third of the participants—was usually temporary. It is likely that this irritation was partly related to difficulty using the electronic cigarette, and that regular reminders on how to use the device resulted in the symptom going away. This symptom could also be imputed to the nicotine present in the liquid. The second most frequently reported adverse effect was temporary fatigue, in 30% of patients. It is difficult to identify whether this effect was fully attributable to the CBD or partially linked to the cannabis withdrawal itself. However, all the adverse effects were mild, which provides additional evidence suggestive that short-term CBD vaping is safe. More widely, there is scientific controversy regarding the risk of long-term electronic cigarette use (53–55). The inhalation of CBD *via* an electronic cigarette should therefore be considered a short-term or transitional option. Furthermore, since the possible mechanisms of action of CBD in CUD are rooted in a reduction of withdrawal symptoms and cravings, the administration of CBD over long periods would not appear to be necessary. Contrary to the perceptions of some CBD users, we do not believe that CBD is the equivalent of opiate replacement therapy for cannabis.

Our study has several biases. It is an exploratory, non-randomized, uncontrolled, open-label study with a small number of participants. It therefore provides some new information, but cannot offer conclusive evidence on the efficacy of inhaled CBD in CUD. The aim of this study was to assess its feasibility in order that a second, larger scale, multi-center, randomized, placebo-controlled study could be conducted if the conclusions suggested that CBD may be effective. Some of the results will enable us to refine aspects of the protocol, for which there were no available scientific data to draw on at the time of its design, such as the daily CBD dose to administer in order to hopefully achieve clinical efficacy. A study has since provided data on this point for oral CBD (47).

The study has a selection bias, evident in the proportion of participants who had already tried a vaping device (75%), although only a minority were active vape users at the start of the study. The proportion of participants who had previously tried CBD was also high (50%). This may have improved treatment retention in patients who were already familiar with vaping and CBD.

This study presents a confounding bias related to the French cultural particularity of co-consuming cannabis with tobacco. We therefore chose to offer the option of adding nicotine in the vaping liquid to adapt to the practices of our target population. We considered that it was unethical not to propose nicotine to accompany the tobacco withdrawal which would inevitably take place with the reduction of consumption in joints, and to prevent an increase in the cigarette consumption of the participants. Indeed, in our population, only one participant didn't use cannabis with tobacco in joints (he smoked it in a pipe), and he was also a cigarette smoker. We observed in fact two cases of smoking cessation, a reduction in the mean number of cigarettes smoked per day by the participants and a decrease in exhaled carbon monoxide levels during the follow-up period. These effects may have been related to the presence of nicotine in the liquids used and the addiction support on offer, plus an addictolytic effect of CBD in smoking, as discussed in the scientific literature (37).

There could be another confounding bias due to the important proportion of participants with a history of psychiatric illness (65% of our population). It is possible that CBD may reduce some psychiatric symptoms, especially anxiety, and that it is through this indirect mechanism that participants with psychiatric conditions reduce their cannabis consumption This confounding bias was mitigated by the need to be psychiatrically stable to be included in the study. To verify this hypothesis in a larger study,

it would be interesting to check if there is a greater proportion of psychiatric illnesses in the participants who respond to CBD.

Clinical studies in CUD share a number of methodological limitations that we also experienced, in particular the difficulty of measuring the amount of cannabis consumed by participants. We do not believe that the proposal to establish a "standard THC unit" (56) is currently applicable to the French context, in which cannabis is obtained illegally, with a high level of variability in product composition and individual consumption practices. While the content of a joint consumed by a given patient is not necessarily comparable to that of another, we decided that this was the unit of measurement for cannabis best suited to our study population. In particular, we were not convinced that all the patients would be able to assess their daily cannabis consumption in grams, and this would still be an unreliable unit of measurement given the variability in the type of cannabis purchased (resin or bud) and in the cannabis content of resin. Another major challenge is how to determine clinically relevant endpoints other than abstinence. A scientific consensus appears to be emerging around the value of research assessing a reduction in consumption rather than abstinence, while acknowledging the difficulty in finding useful endpoints (45, 57, 58): reduction in quantity consumed, reduction in frequency of use, improvement in quality of life, improvement in dependence severity scales etc. However, there is no consensus as to what constitutes a clinically significant reduction in cannabis consumption. In clinical trials assessing the efficacy of vaping or other measures to reduce smoking, the primary endpoint is most commonly a reduction of at least 50% in the number of cigarettes smoked per day (59, 60). We therefore settled on a primary endpoint of a reduction of at least 50% in the amount of cannabis consumed in terms of number of joints per day. The fact that this primary endpoint is based on self-reporting introduces a potential risk of social-desirability bias, although clinical trials in substance use disorders have shown generally high levels of consistency between data reported by participants and objective toxicological data (57, 61). It is interesting to note that despite the undeniable value of aiming for harm reduction, the majority of participants (65%) said at the beginning of the study that they wanted to achieve abstinence from cannabis.

The use of qualitative urine toxicology tests proved to be of limited value during the study, since three patients stopped using cannabis completely, and this occurred at the end of the follow-up, which meant there was insufficient time to check that the urine tests were negative. However, the urine tests would have allowed us to discuss any undeclared consumption of substances other than cannabis with the patient, although this situation did not arise during the follow-up.

Treatment retention was 45% at 12 weeks. This figure is comparable to the retention rates in other clinical studies of patients with CUD (42, 43, 62). This is particularly noteworthy given that the research took place during the COVID-19 pandemic: the French health authorities imposed two strict lockdowns on the French population during the study period, which made it much more complicated to offer outpatient support to the participants.

This research highlights the benefits of CBD in CUD and need to continue evaluating this substance. It also illustrates the benefits of inhalation as the route of CBD administration in patients who already consume cannabis: inhalation can allow users to self-titrate CBD based on their withdrawal symptoms and cravings. A double-blind, randomized, multi-center, placebo-controlled clinical trial is still needed to assess the efficacy of inhaled CBD in CUD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CPP Sud-Ouest et Outre-Mer 1 (South-West and Overseas 1 IEC). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GC designed the study and wrote the first draft of the manuscript. GC and CO organized the database. ED, CL, SL, and AB collected the data. CO performed the statistical analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

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Effects of a Residential Multimodal Psychological Treatment in an Addicted Population, at 6 and 12 Months: Differences Between Men and Women

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The aim of this study is to explore the effects of a residential multimodal treatment intervention for an addict population. We gathered participants from the "Programa Base" (n = 166) of the Solidarity and Reinsertion Foundation of Murcia, and assessed the various problematic areas with the EuropASI at baseline level, 6 months and 12 months of treatment. We found improved outcomes in every area except for Legal Status. In addition, we found differences between male and female participants in their baseline evaluation, as well as between completers and non-completers. In conclusion, this data shows us some changes which occurred in individuals with problematic drug use during treatment, going further into the complex social reality which causes great suffering and damage to people and their families.

Keywords: addiction, substance-related disorders, treatment, retention, gender

INTRODUCTION

Drug use continues to be one of the most persistent threats to health in Spain and Europe, directly and indirectly affecting the well-being of millions of people in our country (1). Understanding of the phenomenon of addictions has increased in recent years, thanks to the continuous effort of professionals and researchers to elucidate the most relevant treatment factors as well as the current commitment to investing in effective treatment approaches (1–3).

There have been several publications over the last 30 years on the evidence of the effectiveness of Therapeutic Communities (TCs) for addiction treatment with publications on this subject in systematic reviews and meta-analyzes (4–11).

The review by Malivert et al. (6), aimed to assess the effectiveness of TC treatment on abstinence and determine its predictive factors. Twelve studies were selected in which 3,271 patients from 61 TCs participated. All studies showed a reduction in substance use during treatment and following discharge. Treatment completion was the best predictor of abstinence at follow-up, though long-term benefits were uncertain. There were important complications when comparing data due to the large diversity between treatment modalities evaluated, duration, and characteristics of the population who attended.

TABLE 1 | Sociodemographic characteristics of sample.

Variable	*N* (%)	*N* men (%)	*N* women (%)
Sex			
Men	129 (77.7)	-	-
Women	37 (23.3)	-	-
Civil status			
Married	26 (15.7)	23 (17.8)	3 (8.1)
Widowed	1 (0.6)	-	1 (2.7)
Divorced	33 (19.9)	20 (15.5)	13 (35.1)
Single	91 (54.8)	74 (57.4)	17 (45.9)
Education level			
Primary	28 (16.9)	22 (17.1)	6 (16.2)
Secondary	51 (30.7)	40 (31)	11 (29.7)
Higher	9 (5.4)	5 (3.9)	4 (10.8)
Legal status			
No legal problems	138 (83.13)	105 (81.39)	33(89.18)
With some legal problem	28 (16.9)	24 (18.8)	4 (10.8)
Employment type			
Full time	99 (59.6)	80 (62)	19 (51.4)
Part-time (stable)	15 (9)	8 (6.2)	7 (18.9)
Part-time (irregular, temporary)	11 (6.6)	10 (7.8)	1 (2.7)
Student	4 (2.4)	3 (2.3)	1 (2.7)
Retired/disability	6 (3.6)	4 (3.1)	2 (5.4)
Unemployed	8 (4.8)	6 (4.7)	2 (5.4)
Safe environment	5 (3)	5 (3.9)	-
Source of income			
Employment	36 (21.7)	27 (20.9)	9 (24.3)
Social security	12 (7.2)	10 (7.8)	2 (5.4)
Social aid	5 (3)	4 (3.1)	1 (2.7)
Penson or social security	28 (16.9)	21 (16.3)	7 (18.9)
Partners, family or friends	46 (27.7)	35 (27.1)	11 (29.7)
Ilegal	1 (0.6)	1 (0.8)	-
Other sources	8 (4.8)	5 (3.9)	3 (8.1)

TABLE 2 | Substance use and clinically relevant variables.

Variable	*n*	%
Retention		
Drop out deliberate	74	44.6
Completers	83	50
Expulsion	6	3.6
Referral	2	1.2
Other reasons	1	0.6
Main consumption substance		
Alcohol	27	16.3
Heroin	10	6
Other opioids/pain relievers	2	1.2
Benzodiazepines and other	2	1.2
Cocaine	49	29.5
Cannabis	8	4.8
Other	2	1.2
More than one substance daily	3	1.8
Alcohol and drugs	38	22.9
Polytoxic addict	4	2.4
Previous Treatments	64	38.6
Associated psychological problems		
Depressed mood	13	7.8
Hostile mood	3	1.8
Anxiety or nervousness	8	4.8
Thought disturbance, paranoid ideation	154	92.8
Attention or memory disturbance	13	7.8
Suicidal ideation	2	1.2

Various studies have found a strong link between treatment duration in TCs and completion, with greater recovery than when treatment is abandoned prematurely (12–17). Therefore, treatment abandonment is of great concern in all addiction treatment modalities (18), and is often most common in the first months (11). This is particularly relevant when we consider that TCs appear less effective than other forms of intervention regarding treatment adherence (18), and that results improve every 3 months that a person remains (7, 19, 20).

In addition to treatment, type and duration influence outcome and results. Recent research indicates that addiction severity, gender, attachment, comorbidity with personality disorders, therapeutic alliance, relationships within TCs, and social and occupational integration are highly relevant variables when predicting treatment results and adherence in the first months (21–34).

The vast majority of studies in systematic reviews and meta-analytic studies were carried out on the American and Australian population, although 2 studies on the Spanish population are also mentioned. In the work by Fernández-Montalvo et al. (35), a long-term follow-up was performed (a mean of 6 years following treatment) of a TC treatment for addictions. A comparison was made between those who completed and who abandoned treatment. The sample comprised 155 subjects (113 who completed and 42 who dropped out). The latter showed a higher and earlier rate of both relapses (83.3 vs. 32.7%) and new treatments for their addiction than the completion group (66.7 vs. 23%). The program was also effective in reducing illegal behavior and improving health status. In the second study by Fernández-Hermida et al. (36), the authors found significant reductions in the use of alcohol and illegal drugs, in illegal behavior, and a large percentage of those assessed, achieved and maintained stable employment at the 3-year follow-up. The main differences were found between the completion group and those who abandoned it with the latter suffering relapses in a much shorter period than the rest.

As well as studies included in reviews, there are relevant works by López-Goñi et al. (37), Pérez del Río (38) and Valero-Agüayo (39), for treatments similar to those analyzed in previous meta-analytical studies (35, 36). López-Goñi et al. (37), described the pre-post treatment evolution of a sample of 112 patients observed in two Spanish TCs. Sample evaluation was with the Addiction Severity Index (ASI), at start and finish of treatment. Sixty nine point seven percent of the sample completed treatment

and 30.3% abandoned it. Results showed a statistically significant improvement in eight of the nine areas evaluated. Only in Physical Health were there no significant changes. The authors highlight that this is possibly due to the high rate of chronic physical illnesses presented by those evaluated. Pérez del Río (38) found that people with better prognosis and who complete 6 months of treatment tend to respond to less unstructured profiles at the social and relational level, have experienced longer abstinence periods, and had significantly lower drug use. On the other hand, Valero-Agüayo et al. (39) observed that the presence of polydrug use, emotional and physical abuse, and numerous family conflicts were factors closely related to abandonment, thus suggesting treatment models that take these variables into account.

Our main aim is to analyze the efficacy of a multicomponent treatment protocol in people with severe substance use disorder, as well as to observe the influence of time in treatment in critical areas (medical health, employment problems, alcohol problems and illegal drugs, social and family relationships, and psychopathological state). Our main hypothesis is that the longer a person remains in treatment, the more pronounced the decrease in addiction severity and other associated problems.

Our second aim is to analyze the relationship between women and men, type of completion, and number of treatments with addiction severity and other associated problems.

METHODS

Participants

The study simple was drawn from the 322 cases attended to between January 2017 and January 2019 in the base program of the Solidarity and Reintegration Foundation of the Region of Murcia. Inclusion criteria were: (a) have substance use problems, (b) participate voluntarily. An exclusion criterion was that participants had not been in treatment for substance use disorder in the previous 6 months.

On applying these criteria, the selected sample was 166 participants (51.55% of the initial population). The mean age of people in treatment was 40.17 years. 22.3% were women. The main substance of consumption in the sample was cocaine (29.5%), followed by joint consumption of alcohol and other drugs (22.9%), and alcohol alone (16.3%). 38.6% reported having received some prior treatment. The mean age and standard deviation at the start of consumption was 26.37 (SD = 21.36) and 21 years of habitual consumption (**Table 1**).

The absence of substance use was assessed by self-report and by random urine sample tests throughout the therapeutic process.

Instruments

Sociodemographic variables: information on user status was gathered through a semi-structured registry interview developed for this work. Sociodemographic data were gathered (gender, age, educational level, employment, legal records) and clinically relevant variables (substances used, family history of use, type of main substance used, years of use, number of previous treatments).

The EuropASI: is the European Version of the Addiction Severity Index, ASI (40) and the Spanish version was used for this study (41), which presents high internal consistency ($\alpha = 0.70$). It is a hetero-applied, semi-structured, clinical interview totaling 159 items, widely used for evaluation and diagnosis of patients upon admission to treatment programs, which explores six areas of special relevance to addiction problems: physical health, employment and resources, alcohol and/or drug consumption, legal status, family and social relationships and psychopathological state. As well as different items for each of these areas, the instrument provides a severity index ranging from 0 (no problem) to 9 (extreme problem), with highest scores indicating the need for treatment.

Treatment Program

The Solidarity and Reintegration Foundation is a non-governmental organization providing treatment and rehabilitation programs for those with substance use problems and behavioral addictions. The program evaluated in this study, the Base Program (BP), is a semi-residential treatment program whose intervention is based on the biopsychosocial model, and whose aims are: (a) achievement and maintenance of abstinence by users, (b) normalization and social reintegration of user regarding work and family, and (c) The adoption of a lifestyle promoting personal autonomy.

The treatment program comprises two phases. The reception phase lasts between 4 and 6 months approximately and is characterized by intensive group work of a cognitive-behavioral type oriented toward maintaining abstinence and adherence to treatment. Users were divided according to therapeutic criteria, providing access to residential treatments to more serious cases, people who could not stay on their own or the family home, or did not have a person of reference to help during the process.

The therapeutic community (TC) phase is conducted in a residential way, providing a micro-society where residents and a team of professionals, as a facilitating instrument, assume different roles and are governed by clear and specific rules, designed to promote the personal evolution of residents. Intervention is focused on analysis of various factors involved in relapse prevention and lasts between 6 and 8 months.

The treatment program consists of various components mainly developed through group dynamics, in daily group and individual support sessions when required, throughout the process. Components are: Coexistence program; Cognitive restructuring; Social skills training; Self-regulation/self-control; Recognition and emotional expression; Reconstitution of personal identity; Restructuring of securities; Relapse prevention; Family therapy; Contingency management.

Data Analysis

Descriptive statistics were first obtained from sociodemographic data and the clinical variables of the sample. To analyze the relationship between sociodemographic and clinical characteristics, independent mean comparisons were performed using the Mann-Whitney U test. To assess results of the program, analysis of comparison of means related by the Wilcoxon signed-rank test was conducted. To calculate the effect

TABLE 3 | Differences between baseline evaluations and 6 months.

	Area	Mean (SD)	Z (p)	*r*	*n*
Baseline	Physical health	3.73 (2.848)	5.290 **(0.001**)**	0.526	101
6 months		2.87 (2.509)			
Baseline	Employment problems	5.71 (3.043)	4.033 **(0.001**)**	0.401	101
6 months		4.54 (2.917)			
Baseline	Alcohol use	6.08 (2.989)	5.778 **(0.001**)**	0.575	101
6 months		4.47 (2.352)			
Baseline	Drug use	7.11 (2.894)	7.029 **(0.001**)**	0.699	101
6 months		5.01 (2.555)			
Baseline	Legal status	2.14 (3.158)	0.135 (0.893)	0.013	101
6 months		2.10 (3.008)			
Baseline	Social/family relations	6.81 (2.114)	4.873 **(0.001**)**	0.485	101
6 months		5.35 (1.802)			
Baseline	Psychopathological state	6.8 (2.413)	5.853 **(0.001**)**	0.582	101
6 months		5.19 (2.279)			
6 months	Physical health	2.87 (2.509)	3,163 **(0.002***)**	0.356	79

*$p < 0.01$. *Bold values are to highlight significant results.*

TABLE 4 | Differences between 6-month and 12-month evaluations.

	Area	Mean (SD)	Z (p)	*r*	*n*
6 months	Physical health	2.87 (2.509)	3,163 **(0.002***)**	0.356	79
12 months		2.58 (2.246)			
6 months	Employment problems	4.54 (2.917)	5,028 **(0.001**)**	0.566	79
12 months		3.41 (2.524)			
6 months	Alcohol use	4,47 (2.352)	5,207 **(0.001**)**	0.586	79
12 months		3.27 (2.191)			
6 months	Drug use	5.01 (2.555)	4,538 **(0.001**)**	0.511	79
12 months		3.56 (2.515)			
6 months	Legal status	2.10 (3.008)	1,245 (0.213)	0.140	79
12 months		1.98 (2.603)			
6 months	Social/family relations	5.35 (1.802)	4,455 **(0.001**)**	0.501	79
12 months		4.41 (2.190)			
6 months	Psychopathological state	5.19 (2.279)	4,988 **(0.001**)**	0.561	79
12 months		4.40 (2.225)			
6 months	Physical health	2.87 (2.509)	5.091 **(0.001**)**	0.566	81
12 months		2.58 (2.246)			

*$p < 0.01$. *Bold values are to highlight significant results.*

size of the non-parametric tests, r ($r = Z / \sqrt{N}$) was used in accordance with the procedure described by Rosenthal (1994) when assumptions to calculate Cohen's cannot be fulfilled.

All analyzes and data treatments were performed using the statistical package SPSS 21.0.

RESULTS

Of the 166 people evaluated at start of treatment, 42.8% abandoned treatment before completion, while 50% remained to the end (see **Table 2**). In the longitudinal analysis of the different moments of evaluation of treatment (baseline, 6 months and 12 months), relevant data was found on the effect of treatment on severity of patients' problems. In comparison between baseline and 6 months, significant differences were found in Physical Health indices ($Z = 5.290$, $p < 0.01$, $r = 0.526$), Employment Problems ($Z = 4.033$, $p < 0.01$, $r = 0.401$), Alcohol Use ($Z = 5.778$, $p < 0.01$, $r = 0.575$), Drug Use ($Z = 7.029$, $p < 0.01$, $r = 0.699$), Social / Family Relations ($Z = 4.873$, $p < 0.01$, $r = 0.485$), and Psychopathological State ($Z = 5.853$, $p < 0.01$, $r = 0.582$) (see **Table 3**), 42.8% abandoned treatment before completion.

Similar decreases were found in severity indices on comparing evaluation at 6 months with that of 12 months, in Physical Health indices ($Z = 3{,}163$, $p < 0.01$, $r = 0.356$), Employment Problems

TABLE 5 | Differences between baseline and 12-month evaluations.

	Area	Mean (SD)	Z (p)	*r*	*n*
Baseline	Medical status	2.87 (2.509)	5.091 **(0.001**)**	0.566	81
12 months		2.58 (2.246)			
Baseline	Employment problems	4.54 (2.917)	5.369 **(0.001**)**	0.597	81
12 months		3.41 (2.524)			
Baseline	Alcohol use	4,47 (2.352)	6.735 **(0.001**)**	0.748	81
12 months		3.27 (2.191)			
Baseline	Drug use	5.01 (2.555)	6.797 **(0.001**)**	0.748	81
12 months		3.56 (2.515)			
Baseline	Legal status	2.10 (3.008)	0.698 (0.485)	0.077	81
12 months		1.98 (2.603)			
Baseline	Social/family relations	5.35 (1.802)	5.677 **(0.001**)**	0.631	81
12 months		4.41 (2.190)			
Baseline	Psychopathological state	5.19 (2.279)	6.315 **(0.001**)**	0.702	81
12 months		4.40 (2.225)			

$^{**}p < 0.01$. *Bold values are to highlight significant results.*

($Z = 5{,}028$, $p < 0.01$, $r = 0.566$), Alcohol Use ($Z = 5.207$, $p < 0.01$, $r = 0.586$), Drug Use ($Z = 6.797$, $p < 0.01$, $r = 0.511$), Social / Family Relations ($Z = 4.455$, $p < 0.01$, $r = 0.501$), and Psychopathological State ($Z = 4.988$, $p < 0.01$, $r = 0.561$) (see **Table 4**).

As for treatment effects when comparing the initial and 12-month evaluations, significant differences were found in Physical Health indices ($Z = 5.091$, $p < 0.01$, $r = 0.566$), Employment Problems ($Z = 5.369$, $p < 0.01$, $r = 0.597$), Alcohol Use ($Z = 6.735$, $p < 0.01$, $r = 0.748$), Drug Use ($Z = 6.797$, $p < 0.01$, $r = 0.748$), Social/Family Relations ($Z = 4.873$, $p < 0.01$, $r = 0.631$), and Psychopathological State ($Z = 4.988$, $p < 0.01$, $r = 0.702$) (see **Table 5**).

Significant differences were found between men and women in several of the EuropASI severity indices (see **Table 6**). A greater severity of problems was observed among women in the Physical Health index (UMW = 1667.5; $p < 0.01$; $r = 0.29$), Social/Family Relations (UMW = 1762.0; $p < 0.05$; $r = 0.19$), and Psychopathological State (UMW = 1756.0, $p < 0.012$, $r = 0.19$), and a greater severity in the group of men in Drug Use (UMW = 1876.0; $p < 0.05$; $r = 0.16$), and Legal Status (UMW = 1903.0; $p < 0.05$; $r = 0.16$).

On analyzing differences found at the start of treatment of those who completed and who abandoned treatment, differences were only seen in Social / Family Relations (UMW = 2349.5; $p < 0.05$; $r = 0.18$) (see **Table 7**). On comparing the group who had previously received treatment with those starting treatment for the first time, significant differences were found in Drug Use at 6 months of treatment (UMW = 934.50; $p < 0.05$; $r = 0.21$) and at 12 months (UMW = 529.00; $p < 0.05$; $r = 0.28$), but notat the beginning.

There are no significant differences between the Medication/No-Medication groups for any EuropASI indices at any evaluation time (Baseline, 6 months, 12 months), except for the index of legal problems at Baseline evaluation (UMW = 2456, $p < 0.05$, $r = 0.17$) and at 12 months (UMW = 438.5, $p < 0.05$, $r = 0.29$), and the index of psychological problems at 6 months (UMW = 709, $p < 0.01$, $r = 0.29$) (see **Table 8**).

There are differences in the EuropASI index of psychological problems in the evaluation of Start (UMW = 2,372, $p < 0.05$, $r = 0.16$) between people who manifested problems with concentration in the previous month and those who did not, and in problems 12 months after treatment (UMW = 435, $p < 0.05$, $r = 0.29$).

No significant differences were found for any of the indices between people who experienced severe depression and those who did not. Nor for those who manifested severe anxiety or who experienced violent behavior.

The difference between pretreatment (baseline) and posttreatment (12 months), in substance use was 3.4 (SD: 2.83), effect size is equal to 1.2 (d), and power is 1 for the final sample.

DISCUSSION

The evaluated sample is similar to those found in other articles in the field of addictions (4, 6–8, 18, 42), commonly finding a high percentage of men, cocaine and alcohol users, and polydrug users. The retention ratio in this study is in line with other research (6, 8, 18).

It is worth noting the high percentage of users presenting psychopathological problems, 92.8% symptoms of mental pathology, far from that found in other studies, which report prevalences of around 50% (24, 43–47). This difference might be due to the ASI not being a diagnostic tool and that its psychopathological area is limited to exploring and providing information on possible problems, i.e., it is a screening tool, although it may also be explained by the fact that those who choose this resource (Foundation for Reintegration...) have a longer and more complex history of consumption. Thus, these data must be taken with caution and this area should be explored in future studies with

TABLE 6 | Differences by sex.

	Area	Mean (SD)	Mann Whitney U Test (p)	*r*	*n* (%)
Men	Medical status	3.41 (2.732)	1667.5 **(0.005**)**	0.29	129(77.7%)
Women		4.86 (2.992)			37 (22.3%)
Men	Drug use	7.44 (2.546)	1876.0 **(0.035*)**	0.16	129(77.7%)
Women		5.95 (3.681)			37 (22.3%)
Men	Legal status	2.36 (3.243)	1903.0 **(0.039*)**	0.16	129(77.7%)
Women		1.35 (2.741)			37 (22.3%)
Men	Social/family relations	6.62 (2.137)	1762.0 **(0.014*)**	0.19	129(77.7%)
Women		7.49 (1.909)			37 (22.3%)
Men	Psychopathological state	6.54 (2.559)	1756.0 **(0.012*)**	0.19	129(77.7%)
Women		7.70 (1.525)			37 (22.3%)

*$p < 0.05$, **$p < 0.01$. *Bold values are to highlight significant results.*

TABLE 7 | Differences by number of previous treatments, and type of discharge.

	Area	Mean (SD)	Mann Whitney U Test (*p*)	*r*	*n* (%)
No prior **T_x**	Drug use (Start)	6.95 (2.973)	3070.00 (0.493)	0.05	102 (61.5%)
Prior **T_x**		7.36 (2.768)			64 (38.5%)
No prior **T_x**	Drug use (6 months)	4.59 (2.520)	934.50 **(0.034*)**	0.21	59 (58.4%)
Prior **T_x**		5.60 (2.519)			42 (41.6%)
No prior **T_x**	Drug use (12 months)	2.98 (2.338)	529.00 **(0.011*)**	0.28	48 (59.3%)
Prior **T_x**		4.39 (2.768)			33 (40.7%)
Voluntary discharge	Social relations/relatives	7.10 (2.185)	2349.5 **(0.027*)**	0.18	71 (46.1%)
Therapeutic discharge		4.86 (2.992)			83 (53.9%)

*$p < 0.05$. *Bold values are to highlight significant results.*

standardized diagnostic tests that can more reliably estimate psychological pathology.

The most striking treatment results have always been found when comparing severity of problems of profiles at start of treatment with results after 12 months. These data correspond to those in other studies on the importance of time spent in treatment (12–17). In this study, the severity of medical problems and those related to illegal substances (EuropASI Medical and EuropASI Drugs) reduced considerably in the first 6 months of treatment. Contrarily, in severity of family/social and employment problems, greater treatment effects are observed in the second period (6–12 months). This more pronounced decrease in the last stage might be due to the fact that vocational training and/or employability workshops do not begin until severity of alcohol and drug use has decreased, as occurs within the area of relationship problems between users and their family members (6, 8, 18). These data, added to the fact that the only difference we found between those completing treatment and those not, was greater severity of family/social problems, supporting the need for treatment modalities that include interventions in this area. These must be developed from the very start as delay until later intervention stages can cause intense emotional burden in users that can lead to premature abandonment of treatment. This is relevant if we consider that the person's level of social and family integration plays a key role in whether they remain in treatment (6, 8, 32, 34, 48, 49).

No variations were found regarding legal problems throughout treatment. We understand this is caused by the low severity of legal problems presented by the collected sample, since other treatment modalities in TCs did find a marked reduction in these problems among prison populations that present high levels of this type PODEMOS QUITAR CONCHA? (8, 50–52).

There are considerable differences between men and women in the entry profile as regards severity of medical, family, psychological, legal problems, and dependence on illegal substances. As the percentage of women in the sample was low, data should be viewed with caution.

In this study, it was found that patients with a history of previous treatments obtain worse results at 6 months and 12 months in the EuropASI Drug Use Index, corresponding to data that indicate better results with fewer treatment episodes (53–56). Some studies mention the difficulty of profiles with several previous failed treatment schedules (54, 55, 57, 58) which may be due to greater severity at start of treatment. Darke et al. (59), found that users who had stayed longer in the same treatment itinerary obtained better results, while those presenting a longer history of previous treatments, and with a similar or even longer time

TABLE 8 | Differences by medication status.

	Area	Means (SD)	Mann–Whitney *U* test (*p*)	*r*	*n* (%)
No_Med	Legal status (Start)	1.6 (2.685)	2,456 (0.037*)	0.17	71 (45.81%)
Med		2.51 (3.389)			84 (54.19%)
No_Med	Psychopathological state (6 m)	4.5 (2.325)	709 (0.006**)	0.29	48 (52.17%)
Med		5.84 (2.145)			44 (47.83%)
No_Med	Legal status (12 m)	2.28 (2.501)	438.5 (0.016*)	0.29	40 (55.56%)
Med		1.16 (2.245)			32 (44.44%)
No_Prob	Psychopathological state (Start)	6.21 (2.601)	1762.0 (0.014*)	0.16	92 (59.36%)
Prob_Con		7.12 (2.329)			63 (40.64%)
No_Prob	Legal status (12 m)	1.71 (2.44)	435 (0.013*)	0.29	39 (54.17%)
Prob_Con		1.81 (2.464)			33 (45.83%)

*$p < 0.05$, **$p < 0.01$.

in treatment often achieved much worse treatment results (26, 29, 54, 55, 57, 58).

As for the study's limitations, a control group could not be included in the research due to the desire to provide users with the best possible treatment without delay, which is a methodological weakness, as well as the absence of longer follow-up. Nevertheless, it provides relevant data on two treatment stages which can help improve the applied protocols.

CONCLUSIONS

The main conclusions are as follows: (a) longer treatment time brings better therapeutic results; (b) severity of treatment areas related to substances and physical health greatly improve in the first months of treatment, while social/ family and employment problems require longer for improvement to be effective; (c) Patient gender influences severity of consumption problems, legal situation, physical health, and the social/family relationships presented and these must be considered when designing interventions; (d) Social-family problems influence retention of treatment and these problems must be addressed from the start to try and prevent premature abandonment of treatment; (e) Those with a longer history of treatment present additional difficulties and these must be determined to avoid early abandonment.

The main aim of this research was to assess the efficacy of the multimodal cognitive-behavioral treatment protocol applied at the Solidarity & Reinsertion Foundation of Murcia (Murcia), and is a first step toward knowing the effects throughout treatment for 1 year in people with consumption problems, delving into this social reality that brings so much suffering and deterioration to people and their families. Information on follow-up at 18 and 24 months is being gathered in this sample, owing to the importance of maintaining improvement achieved by treatment and of obtaining more information on differences between men and women.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Murcia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS-d-P carried out the treatment protocol, collaborated on its application as clinical supervisor, corrected the evidence included in the research, and is a collaborator in the writing of the article. LL-C performed statistical treatment and collaborated in the review of articles. MA-L collaborated in the bibliographic search and writing of the introduction, results, and bibliographical references of the article. AM-P, MC-S, and VF-F carried out part of the search for articles, writing of results, and preparation of tables. CL-S designed the research and collaborated in the proofreading and writing of the article. All authors contributed to the article and approved the submitted version.

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In vivo Experience With NRT to Increase Adherence and Smoking Abstinence Among Individuals in the Criminal Legal System: Study Protocol for a Randomized Clinical Trial

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Background: While tobacco use among individuals involved in the criminal legal system remains 3–4 times higher than the general population, few interventions have been targeted for this population to aid in smoking cessation. Nicotine replacement therapy (NRT) is a relatively effective and accessible smoking cessation aid; however, individuals frequently stop use of NRT early due to side effects and misperceptions about the products. The present study aims to address low medication adherence by examining the efficacy of an "*in vivo*" NRT sampling experience in individuals under community criminal legal supervision.

Methods: Following recruitment through community legal outlets, participants (N = 517) are randomized to either an "*in vivo* NRT sampling" group or a standard smoking cessation behavioral counseling group. The *in vivo* group uses NRT in session and discusses perceptions and experiences of using NRT in real time while the standard smoking cessation counseling group receives four sessions of standard behavioral smoking cessation counseling. Both groups receive four intervention sessions and 12 weeks of NRT following the intervention. The 6-month post-intervention primary outcome measures are smoking point-prevalence abstinence and medication adherence.

Conclusion: This is a novel smoking cessation intervention specifically aimed at increasing NRT adherence and smoking cessation among those involved in the criminal legal system, a group of individuals with high smoking rates and low rates of pharmacotherapy use. If proven effective, the present treatment could be a novel intervention to implement in criminal legal settings given the minimal requirement of resources and training.

This trial is registered with www.clinicaltrials.gov-NCT02938403

Keywords: adherence, tobacco, nicotine replacement therapy (NRT), criminal legal, smoking

INTRODUCTION

Tobacco use remains the leading preventable cause of death and disability in the United States (1). While smoking prevalence has declined to about 14% in 2019 among the general population (2), tobacco use is more than 3–4 times as common among individuals with criminal legal (CL) involvement [i.e., people who have been in jail or prison, on probation/parole, or arrested; (3–7)] (estimated prevalence of 50% to 83%) (8). Individuals in the American CL system who smoke are generally younger at initiation, smoke more cigarettes per day, are 31% more likely to screen positive for nicotine dependence (3), and have high rates of other comorbidities (9, 10). The high rates of smoking among individuals in the CL system suggests that public health messages and interventions have been largely ineffective or not adequately disseminated to this population (5). Additionally, many prisons (for incarcerations exceeding 1 year) and jails (for incarcerations no more than 1 year) have now banned smoking in their facilities (11) and many people who are incarcerated relapse following release (12). However, effective provision of evidence-based interventions for this population offers great public health significance (3, 4, 9, 10, 13), particularly given the health and related risks of smoking upon release. Individuals under community corrections supervision (i.e., probation or parole) represent the majority of the CL population (69%), (14) but have reduced healthcare access due to a lack of health insurance and poverty (15, 16). Since individuals under community supervision are required to have regular contact with CL monitoring agencies, providing smoking cessation services at this point of contact represents an untapped strategy for this under-resourced population who need services and could be routinely treated while under monitoring (17).

A small number of smoking cessation intervention studies have been conducted with the CL population (9, 18). In one, nicotine replacement therapy (NRT) combined with group therapy was provided to a sample of incarcerated women ($N = 250$). Importantly, adherence to NRT was generally low (43% adherent), though it was significantly related to abstinence (10). These results established the initial efficacy of providing NRT for smoking cessation to those in the CL system (10, 19). As mentioned earlier, smoking is now banned in most jails and prisons in the U.S. Additionally, forced abstinence in these smoke-free environments is not enough to maintain abstinence post-release (20). Therefore, interventions targeting the broader CL system are primarily needed as most individuals held in jail are not incarcerated long enough for cessation efforts to be implemented or for prolonged abstinence to occur (21). Unfortunately, few trials have specifically targeted individuals under community corrections supervision to date (22, 23).

Medication adherence can more than triple rates of cessation (24–27). However, medication adherence is particularly low among individuals from under-resourced communities due to negative perceptions of the healthcare system, including less trust in medical providers, lower belief about the efficacy of medication, difficulty accessing services, high costs, and lower health literacy (28–32). Interventions to improve medication adherence in these populations have been identified as the best way to reduce health disparities over other targets such as equalizing access to healthcare or reducing provider discrimination (33, 34). Adherence to smoking cessation pharmacotherapies generally and NRT specifically are similarly poor as most people do not use medications when attempting to quit smoking (35), and among individuals who do use pharmacotherapies, about 69% stop using them prematurely (36). Although brief psychoeducation can improve attitudes toward NRT (37, 38) as well as increase intentions for future use (39), studies measuring behavioral changes (e.g., cessation) did not find psychoeducation alone to be effective (38, 40). This suggests that more hands-on experience, such as trying the cessation medication in the presence of an interventionist, may be necessary to increase medication adherence and subsequent abstinence. This gives the interventionist the opportunity to address any questions or concerns that come up, in real time, rather than asking about the person's experiences trying the medication on their own, when they might have a hard time recalling specific details.

At least two clinical trials have examined NRT sampling and Practice Quit Attempts (PQAs) to increase NRT use and subsequent cessation among outpatient smokers (41, 42). In both, the distribution of and general (i.e., unguided) encouragement to use NRT samples produced positive change in process measures as well as actual cessation. While NRT samples were provided for PQAs, this approach relied on the participant to use the sample on their own without in-session support. Other studies have investigated a more structured sampling experience, providing NRT for in-session sampling, which also led to improved perceptions of medication compared to psychoeducation alone; however, these studies did not investigate subsequent cessation (43, 44). It is possible that providing a guided sampling paradigm of trying NRT samples could also increase adherence to NRT and further promote cessation efforts. Support for this theory is found in exposure therapy whereby exposing a person to an avoided and/or feared but benign situation brings about reduced anxiety when no negative consequences occur (45). Guided, in-session sampling of NRT is particularly well suited to the CL setting, where smokers are available for sustained and structured cessation support. Furthermore, many people in the CL system and other underserved populations are more distrustful of the medical field due to the long history of not having access to healthcare, systemic racism in medical systems, and/or being taken advantage of (8, 46, 47), which decreases the likelihood that they would try cessation medications and ask for help in quitting smoking. In our study, the availability of an interventionist to address side effects in real time and reassure participants that such side effects are normal and expected might make this population more at ease about trying these medications and sticking to them. In addition, given the minimal training and expertise required by the interventionist, the present intervention is especially suitable for these settings as well as other under-resourced environments (48).

Our novel intervention is designed to provide in-session sampling of NRT to increase long-term adherence and cessation. An in-session experience with NRT is a critical aspect of this approach, as it is direct medication experience that appears

to be most strongly associated with adherence and subsequent meaningful clinical outcomes [i.e., smoking abstinence; (41)]. The present article discusses the innovative design of the NRT exposure intervention used in our ongoing clinical trial for outpatients in the CL system (NCT02938403). The trial specifically examines the impact of providing NRT in real time with an interventionist (hereafter referred to as "*in vivo*") sampling to increase later NRT adherence and smoking cessation as compared to a standard smoking cessation counseling group.

METHODS AND ANALYSIS

Study Design and Hypotheses

Participants are randomized to one of two conditions (1:1) testing four 30-min sessions delivered over 4 weeks. A blocked randomization procedure with random blocks sizes 10 and 20 was used to generate the randomization list. The *in vivo* group receives in session NRT sampling with a focus on expectancies for medication and experience using the medication in session. The counseling group receives standard smoking cessation behavioral counseling. All participants receive NRT for 13 weeks with additional nonintervention follow-ups at 1-, 3-, and 6-months post-intervention. Thus, all participants receive almost the same level of evidence-based medication (*in vivo* group receives an additional 2 weeks during sessions 1 and 2); the only differences are the process of introducing it (guided sampling vs. not) and the difference in behavioral sessions (e.g., focus on experience with medication vs. standard smoking cessation behavioral strategies). Specifically, the patch and lozenge were chosen, and the dosage and duration of use were based on standard of care practices (49, 50). These products were chosen because the patch provides a steady dose of nicotine throughout the day while the lozenge is a short-acting NRT, which can help curb cravings in the moment (51). Nicotine gum is another over-the-counter, short-acting option, however using gum requires dentation. Unlike the nicotine inhaler and nasal spray, the patch and lozenge do not require a prescription (44). All procedures are approved by the institutional review board at the University of Alabama at Birmingham (UAB). It is expected that individuals who experience the effects of the medication during sessions will have increased adherence and cessation relative to participants who receive standard smoking cessation counseling.

Importantly, sessions began in person for the first 364 participants, but were changed to primarily remote sessions as COVID-19 precautions were put in place, with 273 participants completing a combination of in-person sessions and some remote sessions. After 6/1/20, the study procedures were modified so that participants are now required to attend an in-person baseline visit with the remaining nine appointments conducted remotely. Participants complete the sessions (*in vivo* or standard counseling) over the phone with study staff and complete all study measures *via* email, text, or verbally over the phone.

Participants

Participants are recruited from the University of Alabama at Birmingham (UAB) Substance Abuse programs including Beacon Addiction Treatment Center (BATC), Treatment Alternatives for Safer Communities (TASC), Court Referral (CRO) Program, drug court, mental health court, community corrections, etc. with flyers posted in relevant locations and *via* snowball recruitment. Interested participants are encouraged to call or email the study team to complete eligibility screening. All study related activities are conducted by research staff only. The recruitment goal for this study is 517 smokers currently under community corrections supervision (not incarcerated). Participants who complete all study appointments receive $440 in compensation.

Potential study participants are phone screened and must be (a) under community criminal legal supervision or will be on probation or parole over the next 6 months, (b) smoking at least 5 cigarettes/day for the past year (c) 18 years of age or older, (d) able to read and speak English, (e) able to provide contact information for at least 2 people if we cannot reach the participant (f) living in an unrestricted environment that allows smoking, (g) able to access a smartphone or a personal email address. Participants must not (h) be pregnant or breastfeeding, (i) have a cognitive impairment or untreated mental illness that interferes with informed consent (based on the judgment of the research assistant if the participant is not responding appropriately or gives any indication that they are not understanding the study), (j) have experienced (within 6 months) post-myocardial infarction or untreated severe angina, (k) have a known sensitivity to NRT or adhesive products (l) exclusively use other tobacco products (e.g., cigars, e-cigarettes; although concurrent use of other tobacco products was not an exclusion criterion), or (m) be currently receiving treatment to quit smoking. It is not an eligibility requirement that participants be motivated to quit smoking. The cutoff of five cigarettes/day was chosen based on the logic that we do not want to enroll people who are light smokers or nondaily smokers for a treatment study, given that the intervention includes use of NRT. Five cigarettes/day is commonly used as a cutoff in many other smoking treatment research studies (52–54).

Once the participants are phone screened eligible, they are invited for an in-person consent and smoking is confirmed *via* an expired Carbon Monoxide (CO) >10 ppm as well as a positive urine cotinine test. Following these final inclusion procedures, they are asked to complete survey measures as part of this baseline appointment. After completion of the baseline procedures, participants are then randomized into the intervention or smoking cessation counseling group. We opted not to include stratification variables given the large sample size in the study. As shown in **Table 1**, side effects are assessed at every time point the participant is expected to be using the NRT. This 37-item questionnaire asks about the most common side effects from using NRT, such as nausea, skin irritation, headaches, etc. All serious adverse events or moderate/severe adverse events are reported to the principal investigator or co-investigator immediately for further guidance. All adverse events will be documented in the research record. Further, all adverse events will be compiled and reported on an annual basis to the IRB and DSMB, as well as NIDA at the conclusion of the study.

TABLE 1 | Study assessment schedule.

Measures or Procedures	BL		Post-Randomization Assessment Schedule								
	Day 0 $20		S1 $20	S2 $20	S3 $20	S4 $20	WK8 $40	WK 12 $40	M1 FU $40	M3 FU $40	M6 FU $40
Screening Questionnaire	X	RANDOMIZATION									
MINI International Neuropsychiatry Interview	X										
Addiction Severity Index-Lite	X										
Everyday Discrimination Scale	X										
Functional Social Support Questionnaire	X					X	X	X	X	X	X
Perceived Stress Scale—10 Item	X		X	X	X	X	X	X	X	X	X
Smoking History	X										
Treatment Interest	X		X	X	X	X	X	X			
Thoughts About Abstinence	X		X	X	X	X	X	X	X	X	X
Smoking Abstinence Questionnaire	X							X			
Abstinence-Related Motivational Engagement	X		X	X	X	X	X	X	X	X	X
Attitudes about Nicotine Replacement Therapy	X					X	X	X	X	X	X
Medication Adherence Questionnaire (MAQ-8)			X	X	X	X	X	X	X		
Fagerström Test for Nicotine Dependence	X										
Wisc Inventory of Smoking Dependence Motives	X										
Questionnaire of Smoking Urges	X		X[1]	X[1]	X[1]	X[1]	X	X	X	X	X
Minnesota Nicotine Withdrawal Scale	X		X[1]	X[1]	X[1]	X[1]	X	X	X	X	X
Cotinine Test	X										
Urine drug screen	X							X			
Pregnancy test	X					X	X	X			
Weekly Smoking Behavior	X		X	X	X	X	X	X	X	X	X
NRT Adherence				X	X	X	X	X	X		
Treatment Satisfaction Survey						X	X	X			X
Perceived Risks of Nicotine Replacement Scale	X		X	X	X	X	X	X			
In-vivo Treatment Expectations	X		X	X	X	X	X	X	X	X	X
Credibility Expectancy Questionnaire (CEQ)			X				X	X	X	X	X
Alliance Questionnaire						X					
Carbon Monoxide Test (CO-iCO smokerlyzer)	X		X	X	X	X	X	X	X	X	X
Carbon Monoxide Test (CO-Vitalograph)	X										
Side Effect Scale	X		X	X	X	X	X	X	X		

BL, Baseline Assessment; S, session; WK, week; M, month; [1]*All participants will complete these surveys twice (at the beginning and end of session) during sessions 1–4.*

In vivo Intervention Group

Participants in the *in vivo* intervention group receive NRT products and counseling focused on their experience of using NRT, including positive experiences, side effects, and smoking cessation expectancies. Intervention participants are instructed to go as long as possible without smoking prior to each *in vivo* session, although participants are not excluded from the study for recent smoking. The rationale for instructing participants to abstain before each session is to demonstrate the effect of NRT for relief of withdrawal symptoms. All sessions are approximately 30 min long and are conducted individually by bachelor's-level research assistants trained by the principal investigator, who is an expert in tobacco treatment, in the *in vivo* and standard smoking cessation counseling interventions.

All participants (regardless of group) complete the Minnesota Nicotine Withdrawal Scale (MNWS) and Questionnaire of

Smoking Urges (QSU) at the beginning of and end of each session. The intervention at each session focuses on their current experience of the product in real time and prior experiences with these NRT products. Feedback is provided on how their craving and withdrawal changes with use of their NRT product(s) (e.g., "your total craving score was 29 and now it is 10 after using the lozenge"). Then, each participant is given instructions on how to use the NRT product(s) between sessions. We solicit positive (e.g., "the patch helps with cravings") as well as negative perceptions of the NRT products (e.g., "the patch makes my arm itch") as the participant samples each product. Participants discuss any side effects they experience after using the product in session and their expectations for the effectiveness of the product for smoking cessation. Safety and efficacy results specific to the product are reviewed with the participant in session. Participants are also encouraged to use the NRT products for practice quit attempts (PQAs) between sessions, which are formally assessed in the questionnaires at the beginning of each session. While a more formal quit attempt is encouraged between sessions three and four, there are no consequences if the participant does not remain abstinent for that session. Since COVID protocols were put in place, the research assistants now provide all NRT products during the baseline appointment and are notifying participants when to start sampling the NRT products prior to their intervention phone appointment.

At session one, participants try the nicotine patch in session under direction of the therapist. Prior to patch placement, they are asked about their perceptions and prior experiences about the nicotine patch. Following patch placement, they are asked about their current experience with the patch (e.g., things they notice, positives as well as negatives, etc.). After this discussion, participants are given seven patches to use for the upcoming week outside of session, with the dose based on number of cigarettes reported at baseline. At session two, participants try a nicotine lozenge following the same procedures as above. At the end of the session, they are given three tubes of 27 count mini lozenges (2 mg). Participants are encouraged to use 8–10 lozenges a day (maximum of 20). At session three, participants try both the patch and lozenge concurrently in session and follow the same procedures in the previous session. They are then given seven patches and three tubes of 27 mini lozenges (2 mg) and asked to set a quit date and make a quit attempt prior to session four. Finally, at session four participants are given 28 patches and 12 tubes of mini lozenges for cessation attempts before their first 1-month follow-up session. For specific session information, see **Table 2**.

Smoking Cessation Counseling Group

Participants in the smoking cessation counseling group receive behavioral smoking cessation counseling based on best practice guidelines (26). This same four-session counseling intervention was used in our previous smoking cessation intervention with participants in the CL system and was found to be acceptable and feasible with this population (48). While this intervention does not focus exclusively on use of NRT, proper NRT use is included as part of any standard behavioral intervention for smoking cessation and is recommended as a best practice guideline when combined with counseling (26). Combination NRT (patch and lozenge) was chosen for this group based on the knowledge that using both a long-acting and short-acting NRT product is the most effective way of using NRT to aid in cessation attempts (51). However, NRT is not used *in vivo* during counseling sessions and participants are not asked to abstain prior to their appointments. Participants are given a supply of seven patches (dose based on smoking reported at baseline) and three tubes of 27 lozenges each (2 mg) to use after their third session. A quit attempt is encouraged between sessions three and four, however there are no consequences if the participant does not make an attempt. At session four, participants are given the same amount of NRT as the *in vivo* group, 28 patches and 12 tubes of lozenges for smoking cessation before their first follow-up. Similar to *in vivo* participants, counseling participants complete the MNWS and QSU before and after each session but are not given any feedback on these surveys. All sessions are conducted by a research assistant trained in the intervention by the principal investigator, who is a clinical psychologist with research and clinical experience in both tobacco treatment and training other clinicians. Sessions are ∼30 min in length matched to the *in vivo* counseling length.

Therapist Training and Fidelity

Therapists for the study are trained on delivering both the *in vivo* and standard smoking cessation counseling protocols by the principal investigator of the study. The one-day training session includes reviewing the importance of smoking cessation, behavioral strategies for quitting, etc. The manual is highly structured to facilitate adherence to the intervention. When counselors covered the topics with at least 90% accuracy during practice, they were able to take study patients on their own. However, if they did not reach the 90% mark, they underwent further training and practice. While it is impossible to blind the intervening therapists to the current behavioral treatment they are delivering, the intervening therapist does not complete the follow-up sessions for the participants they treat. The follow-up assessor remains blind to the intervention delivered to participants. In addition, since most participants are able to complete the measures independently on a surface pro tablet or remotely through REDCap, no opportunity is present for the therapist to influence self-reported changes.

Sessions 1 through 4 are audio recorded by study staff for fidelity checks and 20% of all recordings are reviewed using fidelity worksheets to assess the session therapist adherence to the session. The other staff members trained in the intervention complete the fidelity worksheets for each other, so that no one completes them for sessions they conduct themselves. On each worksheet, there are specified topics that the therapist covers based on the therapist manuals. The reviewer indicates (yes/no) on the worksheet whether the therapist covered the session topics while listening to the audio recording for the session. Staff were trained by the PI using the worksheet to ensure coverage of specific items and topics. Therapists are

TABLE 2 | Session information by group.

Session #	*In vivo* Intervention: NRT Products	Smoking Cessation Counseling Group
1	Patch (∼30 min prior to session), dose is based on CPD at baseline, complete pre- and post-administration withdrawal and craving measures, explore expectancies and side effects of patch use, given 1 week supply for PQAs	Covers benefits of quitting, eliciting social support from family/friends, goals and reasons for quitting and solicit feelings about preparing to quit
2	Lozenge (∼15 min in session use), dose is based on time of first cigarette after waking at baseline, complete pre- and post-administration withdrawal and craving measures, reflect on experience using patch prior week, explore expectancies and side effects of lozenge use, given 1 week supply for PQAs	Focuses on the behavioral factors associated with smoking and the physical symptoms related to nicotine withdrawal. Discuss strategies to cope with craving and withdrawal symptoms
3	Patch and Lozenge (1 week supply of patch and lozenge), complete pre- and post-administration withdrawal and craving measures, reflect on experience using lozenge prior week, explore expectancies and side effects of combination NRT use, assisted in setting a quit day before Session 4	Focus on problem solving strategies to use for successful abstinence including letting friends/family know about quitting, relaxation strategies, soliciting support for quitting, and stimulus control. Received 1 week supply of patch and lozenge and set quit date before Session 4
4	Reflect on experiences with combination NRT prior week. Review problems encountered during quit attempt and solicit solutions. Provided with 4 weeks of patch and lozenge to use for cessation	Focus on gains made during the intervention and discuss the threat of relapse. Discussed problems encountered during quit attempt and solicited solutions. Provided with 4 weeks of patch and lozenge to use for cessation.

When enrollment resumed with new COVID procedures, participants in both groups received all their NRT during the baseline appointment and were subsequently instructed on when and how to use it depending on group assignment.

required to score 90% or higher on the session otherwise they undergo additional training on the counseling interventions. Supervision was given during weekly meetings with staff and the principal investigator.

Follow-Up Procedures

Following the four sessions for both groups, participants complete six brief check-ins to confirm their contact information (weeks 6, 10, 14, 20, 28, and 32) and five follow-up visits (weeks 8 and 12, months 1, 3, and 6), as shown in **Figure 1**. At each follow-up visit, participants complete questionnaires sent through an email/text link or over the phone with study staff. The participant also provides a carbon monoxide reading.

Prior to social distancing measures due to the COVID pandemic, CO was tested at all visits using the Vitalograph CO monitor. After start of COVID distancing measures, participants began being tested at baseline using both the Vitalograph CO monitor and the iCO Smokerlyzer monitor and then are given the iCO to use remotely. The Covita iCO Smokerlyzer is an individual CO monitor that connects to the participant's phone *via* the headphone jack and utilizes a phone application (iCO Smokerlyzer) to measure the participant's CO. The application instructs the participant how to complete the CO testing, asks them how many cigarettes per day (CPD) they are smoking, along with how soon they start smoking after waking up, and provides feedback to the participant about their CO level (e.g., Heavy smoker, Moderate smoker, etc.). Participants share their CO reading results with study staff *via* email directly from the iCO app, which allows study staff to continue to remotely verify smoking status in participants.

At weeks 8 and 12, participants are given instructions and reminders about the remaining NRT (4-week supply at both time points) and are reminded to track their tobacco and NRT use with study calendars until the Month 1 follow-up. At all follow-up visits until Month 6, study staff also verbally confirm pregnancy status for individuals who could become pregnant.

Outcomes

The primary outcome variable will be smoking 7-day point prevalence abstinence confirmed by a CO $\leq$ 3ppm (if measured using the Vitalograph) or CO <6 ppm [if measured using the iCO Smokerlyzer; (55, 56)] at the 6-month follow-up. We will also examine abstinence across the study using the same CO-verified self-reported 7-day point prevalence abstinence. A secondary outcome includes medication adherence (defined as using >80% of doses) during the 10-week intervention period between groups. Adherence is assessed by self-report using timeline followback (TLFB) methods and prior to COVID, included verification through returned patches and blister packs of lozenges. Additional outcomes of interest include quitting across time and incidence, frequency, and duration of quit attempts. If participants are using other tobacco products, this will be reflected in the tobacco-use survey used to determine 7-day point prevalence abstinence for all products (e.g., e-cigarettes, cigars, chew/dip, etc.) as well as in the CO data for products that increase expired CO. In addition, this will be regarded as continued tobacco use and not as quit. Similarly, if participants are smoking other substances (e.g., cannabis) and are over the CO cutoff, regardless of self-report, they will be considered as smoking as we cannot separate the source of smoke through CO at follow-up. This is more conservative but given the high rates of comorbid tobacco and other drug use, particularly cannabis, it is unlikely they would stop one smoking behavior but continue the other.

Sample Size Considerations and Data Analysis

We powered this study based on its primary Aim: intervention effects on 6-month smoking abstinence. Assuming a reference abstinence proportion of 5.8% in the smoking cessation counseling group (based on our previous bupropion trial in the CL population), using a likelihood ratio test of proportions at a significance level of 0.05, a sample size of 250 per group provides

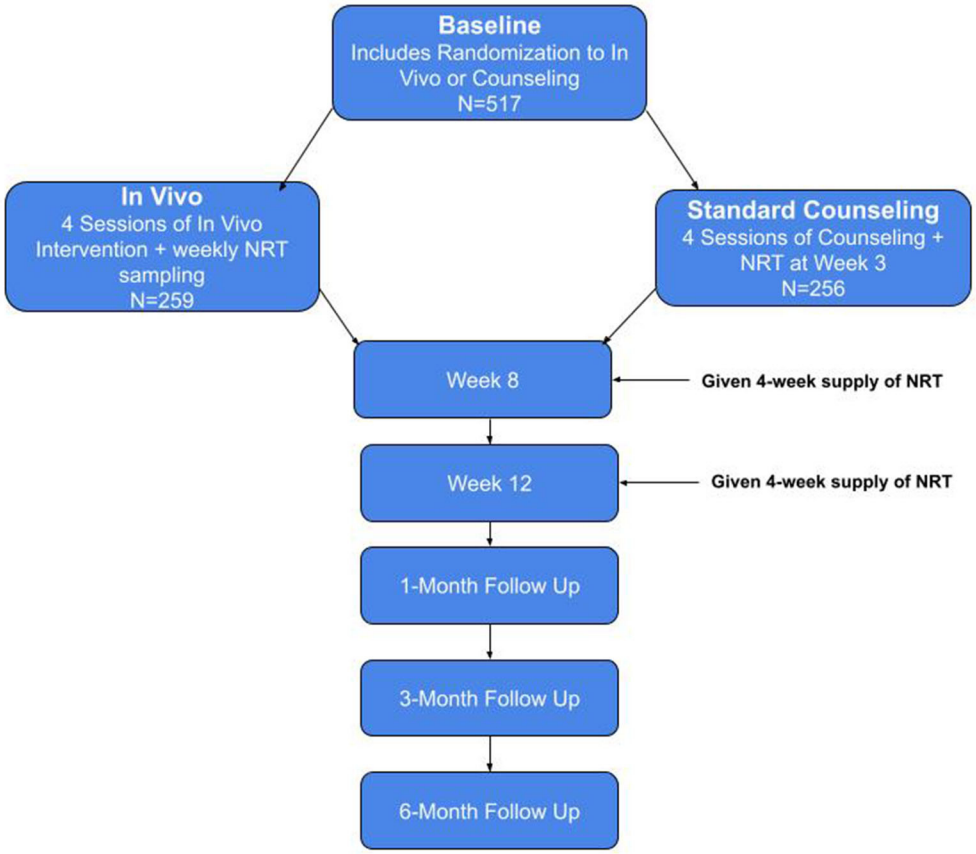

FIGURE 1 | Study flow chart.

80% power to detect a difference of 7.3% (i.e., 13.1% abstinence in the *in vivo* group, OR = 2.45).

To determine whether the abstinence rates differ over time between the two groups, a repeated measures model fitted with a generalized linear mixed-effects model or generalized estimating equations (GEE) will be used, including up to the 6-month follow-up period. This modeling approach includes a covariance structure among the repeated measurements within participants and will use all available data. If necessary, baseline covariates showing relevant baseline imbalances or associated with attrition will be included (57). Measures of effect size (e.g., Cohen's d, Cramer's V) will be used to determine baseline balance in covariates as well as the magnitude of the association between dropout and covariates. We will conduct similar analyses to evaluate differences in incidence rates of 24-h quit attempts as well as longest duration of quit attempt. To examine the secondary outcome of the project (intervention effects on medication adherence during the 10-week intervention period), we will use repeated measures modeling, as described above.

Exploratory moderation analyses will be conducted to determine whether baseline psychosocial variables such as ethnoracial identity, gender, educational attainment, and annual income, or smoking characteristics such as motivation to quit, abstinence self-efficacy, prior use of NRT, and abstinence-related expectancies moderate the relationship between intervention group and abstinence. These analyses will be conducted by fitting models with interaction terms for study group by moderator. We will also conduct mediation analyses (58, 59) to determine if factors such as medication adherence, withdrawal and craving, treatment engagement, and motivation to quit mediate the effect of intervention group on abstinence. These analyses will be conducted using path modeling to partition the intervention effect into direct and indirect. Lastly, we will examine treatment retention (% of people who were not lost to follow-up at 6-months), and engagement (# of study appointments completed) as well as therapist ratings for participants who completed study visits all in person, all remote, or a mixture of both modalities.

DISCUSSION

Significance

The present intervention evaluates whether *in vivo* sampling of NRT can lead to increased smoking abstinence rates compared to standard behavioral smoking cessation treatment among individuals in the CL system. As mentioned earlier, both groups receive NRT although only the *in vivo* group receives guided

and structured sampling in real time with a counselor. If the proposed hypothesis is supported, this intervention could serve as a novel strategy that improves NRT adherence in a quit attempt among individuals in the CL population. The protocol outlined above is feasible to conduct in a wide variety of settings and requires minimal training from staff. In fact, non-therapist, bachelor's-level research assistants trained on both interventions following a therapist manual are the individuals responsible for administering the intervention, underscoring the translatability of this intervention in under-resourced settings. Specifically, the findings will especially benefit individuals involved in the CL system, a population for which smoking cessation interventions are lacking and tobacco use prevalence is high. The low cost and availability of NRT in the U.S., in addition to the limited resources necessary for the intervention, make it easily implementable in community programs as well. Furthermore, the intervention could also be implemented in other settings, such as homeless shelters and hospitals, as those are opportune locations to intervene with under-resourced populations with high smoking rates (60, 61). Initially, training members of the community in this intervention would be required but in the long run, given the impact of smoking on one's health and quality of life, the benefits outweigh the initial costs. While this intervention is specific to NRT, the protocol could potentially be adapted to other smoking cessation medications with low adherence [e.g., varenicline; (62)] as well as other health conditions (e.g., diabetes management) where medication adherence is low.

Remote Research Implications

General Methodology

While the present intervention was initially intended to be conducted as an in-person intervention across all study time points, recruitment and study procedures were adjusted to limit staff-participant contact given the development of the COVID-19 pandemic. Therefore, the intervention was modified to include one initial in-person baseline visit (primarily to verify smoking status and provide participants with the treatment manual, iCO monitor, and NRT products), with the remaining visits being conducted remotely. The circumstances of the pandemic led to the realization that some research procedures might benefit from the convenience and versatility of remote methods. For example, an increasing number of assessments are now being completed through platforms such as REDCap and Qualtrics, and it is plausible that entire interventions could be adapted to other remote modalities (i.e., phone calls, videoconferencing;53). In addition, consenting procedures as well as recruitment advertising can be easily performed remotely (63). Our team's adaptations for this study suggest that it is feasible to not only deliver smoking cessation interventions and counseling over the phone, but also to give smokers instructions on how to use NRT remotely, even in difficult to reach populations such as the CL population. If medication adherence and cessation outcomes are similar or better for those who complete study procedures remotely, these findings could provide support for moving to a more remote model of research. We plan to conduct a secondary data analysis to compare recruitment rate and retention between those who completed the study pre-pandemic to those post-pandemic.

Remote CO Collection

When the study began, carbon monoxide (CO) readings were captured using a Vitalograph CO Monitor. In order to be eligible for participation, participants' CO reading must be >10 ppm at baseline, and if their CO reading is 3 ppm or less (as measured by the Vitalograph) at follow-up assessments, they are considered abstinent from cigarettes. The study protocol was modified as in-person recruitment resumed. Since the new procedures included only one in-person visit, adjustments were necessary so study staff could continue to monitor the participant's smoking status remotely. Study staff continue to use the Vitalograph at the in-person baseline visit as well as train participants to use a take-home device, the Covita iCO Smokerlyzer as mentioned earlier. Study staff assists the participants with downloading the app, setting up an account, and walking through the procedures to complete a breath sample using the participants' own phones at the baseline appointment. The recommended cutoff to determine abstinence with this device is <6 ppm (55, 56).

Therapeutic Interaction

The central premise of the presented *in vivo* exposure is to have a trained bachelor's level therapist present while the participants try the cessation medication and explore expectancies and their experiences with using NRT. As previously mentioned, the therapist encourages participants to provide feedback (both positive and negative) on the use/experience of the medication, helps address any possible side effects, and provides additional product information. It is possible that this therapeutic interaction may be affected by the modality of the interaction (64, 65) (i.e., in person vs. remote). While therapeutic alliance may be comparable in remote vs. in-person sessions, each modality has specific challenges. For example, in-person sessions bring with them the logistical challenges of traveling to an in-person appointment, while a barrier to remote sessions could be limited access to technology or low technology literacy.

Limitations and Strengths

While the intervention described presents numerous benefits and provides novel contributions to the field, several limitations should be noted. One potential limitation is that the intervention is not particularly tailored to the needs of the CL population. While it cannot be overlooked that those in the CL system have many important needs (e.g., financial, housing, and employment assistance), smoking cessation interventions remain extremely important (3, 4) especially given the negative health effects of smoking. Though these structural barriers cannot be fixed with a single intervention, evidence suggests that medication adherence is a critical target for increasing abstinence (33, 34) and that experience with smoking pharmacotherapy may be an important way to improve medication adherence in this population (23). With limited access to healthcare resources for extended periods of time, implementing a smoking cessation treatment plan into CL operations gives individuals the otherwise difficult-to-access opportunity to get help quitting smoking, which will ultimately

lead to better health outcomes. It can also be argued that another weakness of the study is that the treatment is not imbedded in the community corrections system. However, this is a limitation inherent in most research that tests the efficacy of a new approach prior to expanding into more implementation science research, in this case with the community corrections staff.

An additional limitation of the present intervention could be that it is not intensive enough to promote a change in smoking behavior. A sampling intervention such as this may not provide the intensive and prolonged treatment that is necessary for a chronic relapsing condition such as smoking (66). However, time and resource-heavy interventions are unlikely to be implemented in busy clinical or low-resource settings. The proposed intervention was designed to be brief and simple enough to be implemented in busy settings by non-therapist providers but still intensive and targeted to encourage behavior change. While the PI is not a Tobacco Treatment Specialist (TTS) and the staff were not sent for specific TTS training, they are a clinical psychologist with research and clinical experience in both treating and training other clinicians about tobacco treatment,. Furthermore, RA level staff completed the counseling treatment fidelity ratings rather than a clinical supervisor or an outside clinician. Finally, as previously mentioned, intervention procedures were adapted in order to reduce staff-participant contact as the COVID-19 pandemic evolved. While necessary, these adjustments (e.g., primarily conducting remote sessions) could negatively affect the *in vivo* experience and impact the therapeutic interaction. Additionally, another potential issue in the study is the ability to retain participants until study end. Oftentimes people in the CL population have unpredictable lives, where unstable housing situations, cell phone access, transportation, etc. can impact participants' ability to adhere to the study protocol (67). Missed appointments are expected to be similar to our previous study (25–30% missed appointments at any point up to 6 months post intervention). The analytical approach will use all available data adjusted for characteristics relevantly associated with attrition, if any, and thus decreasing potential bias from missing data (57).

Nevertheless, the integrity of the intervention is generally maintained through phone calls with participants, where they can share feedback and discuss questions with the study staff. Further, with the use of the iCO, biochemical verification of smoking status is maintained at all study visits, a significant strength. A final strength of this study was the comparison group (four 30-min behavioral smoking cessation counseling sessions); thus, if the *in vivo* intervention shows stronger cessation results over the current standard, this will provide an important advance in smoking cessation treatment.

CONCLUSION

The presented intervention seeks to improve NRT adherence and smoking cessation over current best practice guidelines. The intervention is delivered onsite where individuals commonly attend to check in for CL supervision. Furthermore, the intervention was adapted due to COVID-19 restrictions by pivoting to remote methods. As such, the current study presents a compelling and innovative contribution to the literature with implications for smoking cessation, NRT adherence, and remote methodologies.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UAB Office of Institutional Review Board (University of Alabama at Birmingham). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PH, AA, AL, MC, and KC designed and planned the study. AA performed the calculations and verified the analytical methods. AF and JB ran the study visits. EH, SMC, AF, JB, and KC wrote the manuscript with input from all authors.

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Theta-Burst Stimulation Combined With Virtual-Reality Reconsolidation Intervention for Methamphetamine Use Disorder: Study Protocol for a Randomized-Controlled Trial

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Background: Craving associated with drug-related memory is one of the key factors that induce the relapse of methamphetamine (MA). Disruption or modulation of the reconsolidation of drug-related memory may serve as an option for clinical treatment of MA addiction. This protocol proposes to use virtual reality (VR) to retrieve drug-associated memory and then use transcranial magnetic stimulation (TMS) at the neural circuit that encodes the reward value of drug cues to provide a non-invasive intervention during reconsolidation. We aim to evaluate the effectiveness of TMS treatment after VR retrieval on the reduction of cue reactivity and craving of MA.

Methods: This is a randomized, double-blind, sham-controlled, parallel group trial, targeting participants with MA use disorder aged from 18 to 45 years old. Forty-five eligible volunteers in Shanxi Drug Rehabilitation Center will be recruited and be randomly allocated into three parallel groups, receiving either 1) MA-related cues retrieval in VR combined with active TMS (MA VR scene + TBS) or 2) sham TMS (MA VR scene + sham TBS), or 3) neutral cues retrieval in VR combined with active TMS (neutral VR scene + TBS). Two sessions of post-VR-retrieval TBS will be scheduled on two separate days within 1 week. The primary outcome will detect the memory-related activity by the electroencephalography (EEG) reactivity to drug cues in VR scenes. Secondary outcomes are the self-reported MA craving in VR scene, the physiological parameter (cue-induced heart rate) and the scores of psychological questionnaires including anxiety, depression, and mood. All primary and secondary outcomes will be assessed at baseline, 1-week, and 1-month post-intervention. Assessments will be compared between the groups of 1) MA VR scene + TBS, 2) MA VR scene + sham TBS and 3) neutral VR scene + TBS.

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Discussion: This will be the first study to examine whether the TMS modulation after VR retrieval can reduce self-reported craving and drug-related cue reactivity. It will promote the understanding of the neural circuit mechanism of the reconsolidation-based intervention and provide an effective treatment for MA use disorder patients.

Clinical Trial Registration: [Chinese Clinical Trial Registry], identifier [ChiCTR1900026902]. Registered on 26 October 2019.

Keywords: cue reactivity, drug craving, methamphetamine use disorder (MUD), reconsolidation-based intervention, theta-burst stimulation (TBS), transcranial magnetic stimulation (TMS), virtual reality (VR)

INTRODUCTION

Methamphetamine (MA) is a potent psychostimulant highly addictive for its euphoric and stimulant effects. It is the most prevalent drug of abuse in China accounting for more than 50% substance users. The number of MA users exceeds one million according to an official survey conducted in 2020 (1) while there is no established therapy for MA dependence (2). A core symptom of MA use disorder (MUD) is craving that lingers even after a long-term abstinence. Craving for MA positively correlates with the severity of MUD (3) and predicts relapse (4). Craving can be induced by cues and contexts associated with drug-related episodic memory (5). The vivid and multi-sensory episodic memory formed through repeated MA use persists after abstinence and drives craving (6), suggesting that intervention on drug-related episodic memory may reduce craving and contribute to relapse-prevention of MUD.

It has been postulated that long-term episodic memories could be modified during a time window called "reconsolidation" after memory retrieval (7, 8). Within the reconsolidation window, memories could be updated, strengthened, or weakened by manipulation of the electrophysiological or neurochemical activity within the neural network encoding the retrieved memory (7, 9). A feature of reconsolidation interventions is that a single or limited numbers of interventions can generate long-term effect for weeks or even months (10–14). Particularly, post-retrieval intervention during reconsolidation reduces the emotional or motivational value of reward cues embedded in episodic memories without disrupting the cognitive component of the cue-reward associative memory (15). Compared to a general reward cue, the motivational value, or incentive salience, of MA cues is stronger and more enduring. Thus, a major difficulty is how to reactivate and destabilize drug-related memory to make it more labile and susceptible to updating. We believe that virtual reality (VR) can reactivate MA-using memory because a vivid, immersive, and interactive virtual scenario carries more contextual information than pictures or videos, which can trigger re-experiencing reward-related memory and potent cravings (16–19). Therefore, we propose that the use of VR to retrieve memory and an MA-craving state provides the possibility for the subsequent intervention.

The reconsolidation of drug-related episodic memory recruits the medial prefrontal cortex and basolateral amygdala (BLA) circuit (20–22) where local pharmacological intervention during reconsolidation can degrade the emotional/motivational impact of the drug-related cues (15). The medial prefrontal cortex is a major cortical center involved in value computation and representation with its multiple sub-regions conducting varied functions (23, 24). The orbitofrontal cortex (OFC) is critical for encoding and updating the incentive value of reward cues in a state-based manner by a reciprocal connection with the BLA (25–27). Clinical studies in substance users found that the OFC dysfunction leads to impaired motives for general rewards but an increased motivation for addictive drugs which gradually develops into a pathological substance craving (28). In addition, inhibition of the OFC or disruption of the OFC-BLA connectivity reduces context- or cue-induced drug seeking (28–31). Although the current evidence supports an idea that the OFC intervention has an immediate effect on cue-induced craving, there is no report on whether inhibition of the OFC can produce a sustained effect to reduce drug-seeking.

Transcranial magnetic stimulation (TMS) is a non-invasive method to modulate neural activity on cerebral cortex by generating a magnetic field close to the scalp over the target brain region (32). TMS with different parameters and stimulation sites can induce long-term changes that facilitate or reduce the activity of neurons or circuits (33). It has been applied as a physical treatment to many neurological and mental disorders such as major depressive disorder (34), obsessive-compulsive disorder (35), and post-traumatic stress disorder (36). Studies with TMS intervention targeting the OFC are rare but their encouraging results show that self-reported cravings for alcohol (28), cocaine (28), or smoking (37) were reduced immediately after OFC or related prefrontal cortex stimulation. Notably, a study on TMS interventions for MA patients compared the effects of stimulation targeting the dorsolateral prefrontal cortex (DLPFC) or ventromedial prefrontal cortex (vmPFC) or both regions for 2 weeks and found that all three treatments reduced MA craving, but TMS over the vmPFC or both yielded a shorter respondence time and a more pronounced effect on sleep quality (38). Another study for alcohol users showed that 10 days of medial prefrontal cortex TBS reduced the connectivity between multiple brain

Abbreviations: BLA, basolateral amygdala; EEG, electroencephalography; MRI/fMRI, Magnetic Resonance Imaging/functional Magnetic Resonance Imaging; MUD, Methamphetamine Use Disorder; OFC, Orbitofrontal Cortex; TMS, Transcranial Magnetic Stimulation; TBS, Theta-Burst Stimulation; VR, Virtual-Reality; VAS, Visual Analog Scale.

regions in reaction to alcohol cues as well as alcohol drinking up to 3 months after TBS treatment (39). This encouraging report suggests that neuromodulation like TBS on the neural circuit mediating reactivity to addictive drug-cue may achieve a sustained inhibitory effect on drug using.

The purpose of this protocol is to design a set of clinical treatments to obtain a sustainable inhibitory effect on the craving for MA after a limited number of interventions. We propose that TMS stimulation of the OFC within the time window of MA-related episodic memory reconsolidation will produce a continuous reduction in craving elicited by MA-related cues or context. In specific, we will use theta-burst stimulation (TBS), a new pattern of TMS, to modulate the activity in the OFC because of its advantage for stronger effects with shorter duration compared to conventional repetitive TMS (40). We will choose continuous TBS (cTBS) due to its promised effect on depression of cortical excitability (22, 31, 33). It has been delivered to the medial prefrontal cortex to decrease reactivity to alcohol-related cues and reduce drinking behavior in a recent studies (39). And cTBS has been used to disrupt OFC network activities in previous studies (41). Since an effective activation of episodic memory is important in reconsolidation-based treatment (42, 43), a series of vivid and immersive VR scenes related to MA using will be present for memory retrieval and craving self-rating (43–45). In addition to self-report craving, the cue-related electroencephalogram (EEG) activity in the VR scene will be recorded as an indirect measure of the degree of memory retrieval and craving (43, 46, 47). Compared to neutral scenarios, the incentive salience of drug-related cues is stronger to draw drug user's attention (48, 49). Attention bias for drug-related cues is associated with subjective craving and tendency to approach drug-related cues (50, 51), indicated by abnormal EEG activities of prefrontal cortex. For example, two studies reported that MA users showed specific EEG features induced by MA-related scenes presented by VR, such as decreased gamma activity in OFC and right DLPFC (52) and reduced EEG power in delta, theta, and alpha bands (53) comparing to neutral scenario. In addition, processing alcohol- or smoking-related cues coincided with surged frontal beta-band activity in binge drinkers (54) or smoker (55); the increased beta-band activity in response to the drug-related cues is associated with enhanced attention and alertness. A recent study further showed that a higher level of synchronization of medial prefrontal cortex for the beta-band activity in 1–3 months abstinent MUD group, compared to groups with longer or shorter abstinence. Meanwhile, MA craving was higher in the 1–3 months abstinence group than other groups (56). This finding suggests that increased prefrontal beta activity may serve as a robust indicator of MA craving.

In summary, we design a randomized-controlled study of memory reconsolidation-based TBS intervention for people with MUD. It aims to investigate the short-term and long-term effects of TBS treatment on reducing cue-induced craving and updating memory-related EEG reactivity for MUD patients. Meanwhile, the physiological parameter such as cue-induced heart rate and possible co-variables such as emotional and mental state will be considered.

METHODS/DESIGNS

Study Design

This is a randomized, sham-controlled double-blind study. Participants will be randomly assigned by main investigator to three parallel groups using computer-generated random numbers with a 1:1:1 allocation ratio, either receive (1) MA-related cues retrieval in VR combined with active TMS (group A: MA VR scene + TBS) or (2) sham TMS (group B: MA VR scene + sham TBS), or (3) neutral cues retrieval in VR combined with active TMS (group C: neutral VR scene + TBS). Participants, outcome assessors, and data analysts will be blinded to the group assignment during treatment sessions. The doctors delivering TMS treatment will know the allocation sequence but will not be involved in the assessment. Once treatment is completed, participants will be asked to guess the specified intervention they have received to determine the actual effect of TBS. Then the clinical evaluator will debrief the participants about the study procedures. The two "VR retrieval–TBS" treatment sessions will be scheduled in 2 days within 1 week using an MA-related or neutral VR scene. Clinical, psychological questionnaires and EEG will be carried out at baseline (T0), each treatment session (T1/T2), the week of the last treatment (T3) and over 1 month after treatment (T4), as shown in **Figures 1**, **2**. This protocol follows SPIRIT recommendations.

Study Setting

This clinical trial will be conducted in Shanxi Drug Rehabilitation Center (Taiyuan, Shanxi Province, China) involving the "VR retrieval–TBS" sessions and a series of assessments (as described in outcome measures).

Participants

Participants with MUD in Shanxi Drug Rehabilitation Center will be voluntarily recruited to this treatment. After initial confirmation, eligible participants will then be required to sign an informed consent. The number and reasons of exclusion individuals, as well as those who reject or withdraw consent will also be recorded. *Inclusion criteria:* Selected participants will have to (1) be clinically diagnosed with Amphetamine-Type Substance Use Disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, (2) abstinence periods at least 2 weeks without obvious withdrawal symptoms (e.g., drowsiness and dysphoria), (3) be aged 18 and 45 years old, and be right-handed, (4) be able to speak and read Chinese, (5) sign a consent form before intervention procedure.

Non-inclusion criteria: Participants meeting at least one of the following criteria will not be enrolled in this study: (1) meeting the diagnostic criteria of any other psychiatric disorder under DSM-5; (2) using other kinds of drugs (e.g., heroin, cocaine) in the past 30 days; (3) having contraindications to TMS treatment (head trauma, epilepsy or the history of epilepsy, metal implant, pregnancy and so on); (4) having a history of mental illness or a family history of mental illness; (5) be insensitive to VR scene (identified at the baseline); (6) having received psycho-therapy or TMS intervention in the last 6 months; (7) receiving medication treatment recently; (8) illiteracy; (9) having visual or hearing

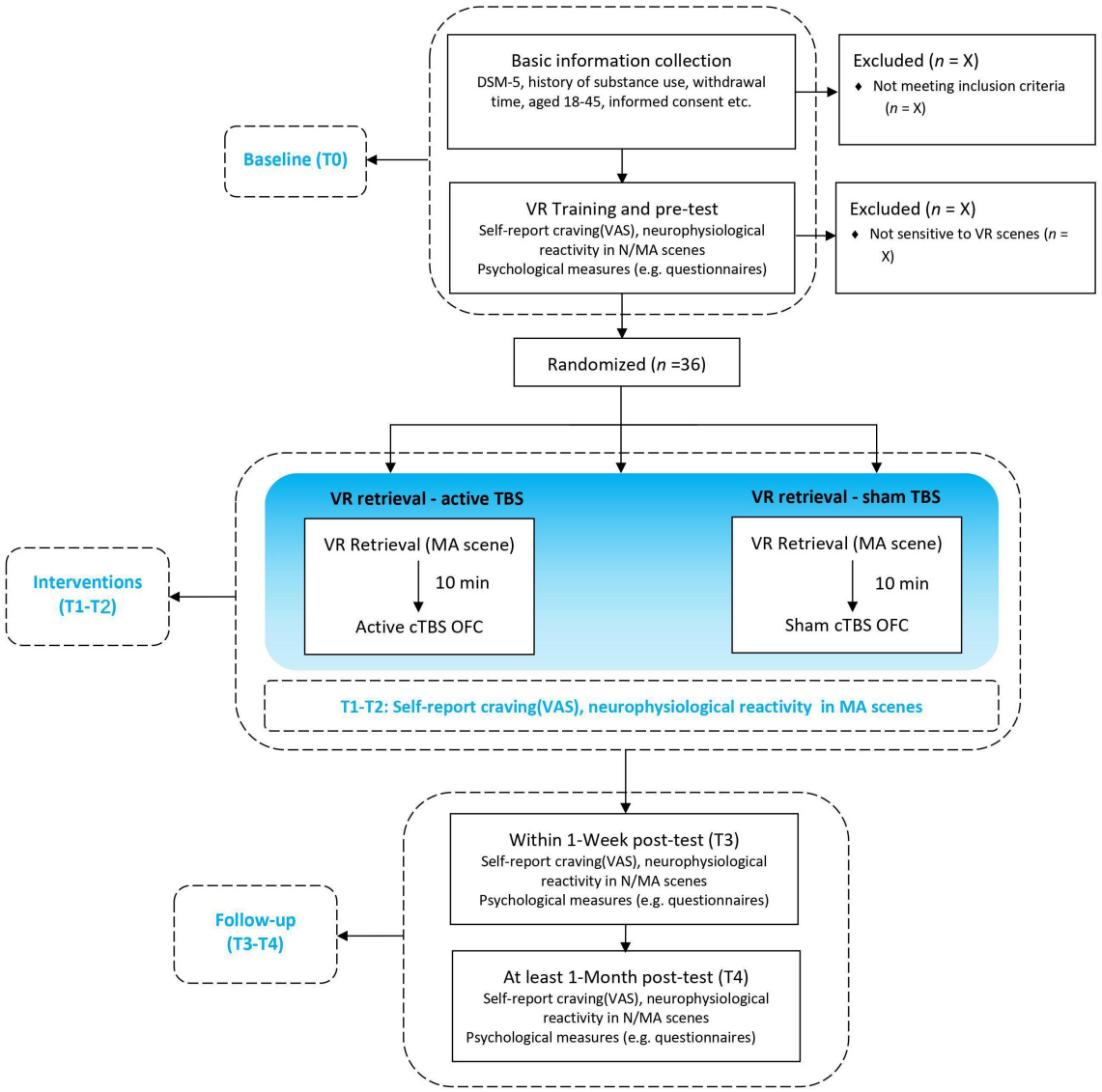

FIGURE 1 | Flow chart of the study design. VR, Virtual Reality; N/MA scenes, neutral/methamphetamine scenes (displayed by VR); cTBS, continuous theta-burst stimulation; OFC, orbitofrontal cortex; neurophysiological reactivity including electroencephalogram (EEG) activities and electrocardiography (ECG) activities in outcome measures.

problems; (10) the individual threshold of TMS was higher than 50% of the maximum output of the TMS equipment; (11) scheduled to receive psycho-therapy or medication treatment for the next 2 months. *Exit criteria:* Participants will be allowed to withdraw from the clinical trial if they (1) voluntarily wish to stop the TBS sessions; (2) can hardly tolerate any aversive reactions (e.g., itching, numbing) or have a desire for other treatments; (3) do not complete the TBS sessions for other reasons; (4) suffer from worsening symptoms such as enhanced craving.

Intervention

The "VR retrieval–TBS" intervention will be given twice within 1 week. Each intervention session contains a MA-related VR scene to retrieve memory (or a neutral VR scene in a control group), a 5-min TBS treatment, and a 10-min interval in between them to conform with the suggestion that a 10-min reconsolidation window may improve the effectiveness of the subsequent intervention (8, 57). A short TBS trial will be delivered before the full-length treatment to decrease risks and improve clinical adherence. The pulse intensity of TBS will be assigned according to identified individual resting motor threshold (RMT).

VR Retrieval

Two types of VR scenes containing a series of neutral or drug-cues respectively will be presented in this study. As introduced in our previous study (43), the VR neutral scene for VR interaction practice at the first time that the participants using VR devices

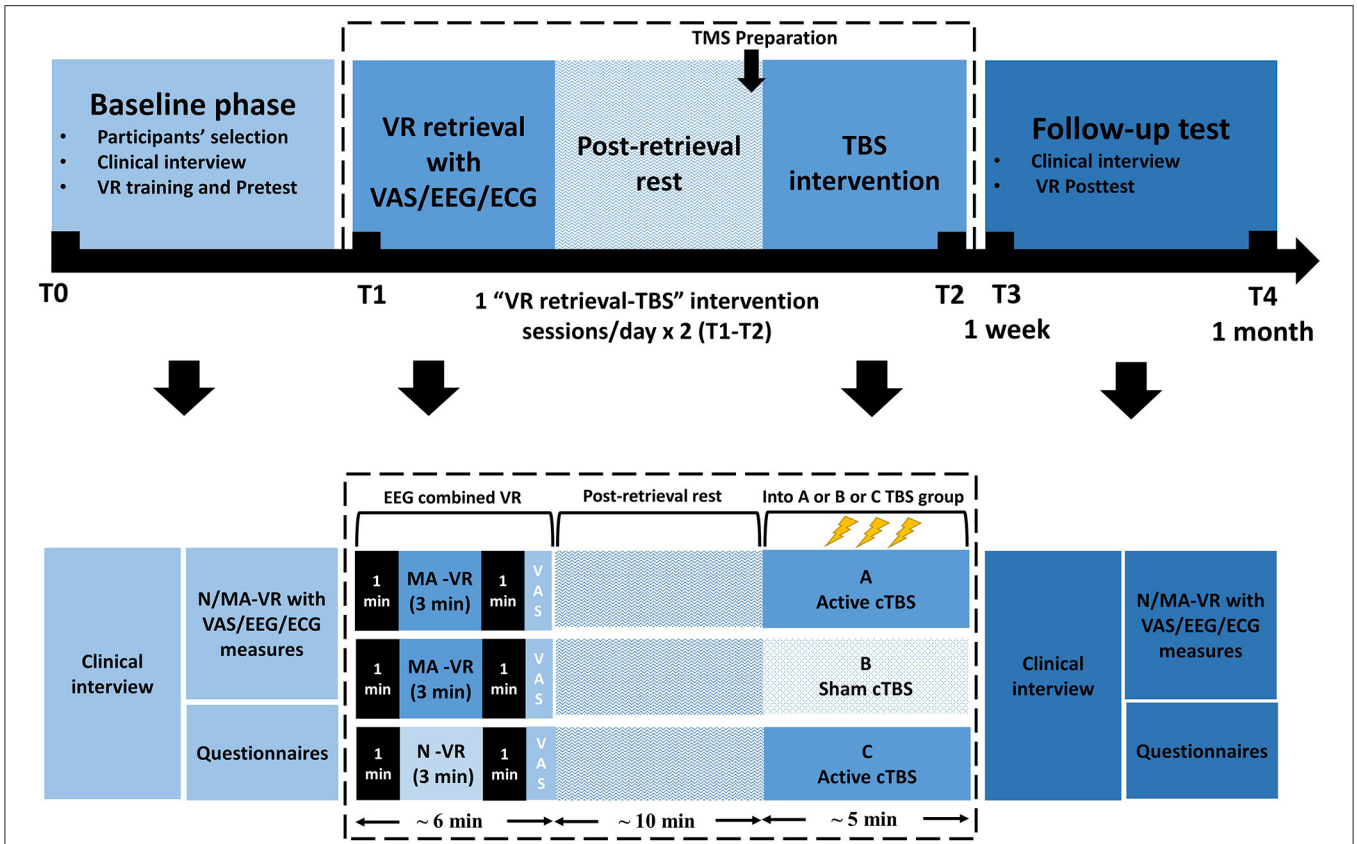

FIGURE 2 | Participants' timeline. VR, Virtual Reality; cTBS, continuous theta-burst stimulation; N/MA-VR, neutral/methamphetamine scenes displayed by VR; VAS, visual analog scale; EEG, electroencephalography; ECG, electrocardiography.

will be, a room with a desk, two spheres, two cubes, two cylinders, a laptop, and a visual analog scale (VAS) presented on the wall of the room. The spheres, cubes and cylinders are interactive, which means they can be picked up or stacked in the VR environment using the handle. This scene for practice will be presented once for 5 min. Another neutral scene will be presented in the baseline test and post-test. The neutral scene will be presented for 3 min followed by MA scenes after a 1-min interval of darkness in between. This neutral scene is a room with a sofa, a coffee table, and a standing lamp. There are about 50 triangle, square, or cylindrical blocks on the coffee table, about 10 cm in diameter. All the blocks are interactive. There are two MA scenes. Both scenes will be presented in the baseline test and the post-test, each 3 min, with a 1-min interval in between. The first MA scene is a room with a sofa, a coffee table, a standing lamp, a wardrobe, and a cabinet. There are many items on the coffee table, including a small bag of MA, a roll of foil, a piece of foil, lighters, plastic beverage bottles, paper money, straws, tools for diluting and filtering MA (a beverage bottle with straws and filters), a cellphone and a laptop. A video of playing a card game is played on the laptop screen. There is a TV hanging on the wall, which can play dance music or gambling game videos through the VR handle. The second MA scene is a room with a bed, a coffee table, and a chair. The items on the coffee table are similar to those in the first MA scene. There is a male or female avatar on the bed doing a series of actions of taking MA. All sofas or beds in the virtual scene have seats of similar heights at the corresponding positions in the real room. The MA-related VR scenes that we would like to use have been validated for their effect on MA memory retrieval based on the data in our lab and previous studies (58). In the baseline test and post-test, after the three scenes (neutral, MA1, MA2), the VAS is presented on the wall of a room in VR. Two groups (MA VR scene + TBS, MA VR scene + sham TBS) will view either the first or second MA scene prior to TBS treatments. Another group (neutral VR scene + TBS) will view a neutral VR scene before TBS treatments. Each scene for memory retrieval will last 3 min at each treatment session with 1 min pre-dark and 1 min post-dark, ended by an embedded VAS for self-reported craving rating. Real-time EEG for brain activity will be recorded while the presentation of VR scene (see *Outcome Measures*).

All VR scenes will be displayed by HTC VIVE VR system containing a wired headset (110 degrees, 1,080 × 1,200, 90 Hz) and a wireless handle controller to provide participants with direct, realistic interactions. With a head-mounted display, participants wearing a headset will immerse into the VR scenes. The wireless controller will also be accessible for participants to interact with objects in the VR scenes and rate VAS. The

VR scenes will be monitored by a care provider on a desk computer (Alienware 15-R2748, i7-7700HQ 16G 256GSSD+1T GTX1070 8G discrete graphics FHD). These VR scenes have been developed by our collaborative team with unity 3D and used in our previous study (43).

TBS Protocol

Target to Stimulate

Refer to related research and large-scale Magnetic Resonance Imaging/functional Magnetic Resonance Imaging (MRI/fMRI) data from https://neurosynth.org/, the OFC, functioning (including both orbital and media area) with encoding specific stimuli value (59, 60) has been located with an averaged MNI coordinates (-4, 36,−18). Following previous suggestion (61), the stimulated site targeting OFC will be located according to the standardized international EEG 10–20 position (Fp1). This brain area will be labeled on an EEG 10 - 20 system cap. The coil will be placed tangent to the scalp at the contact point (**Figure 3**). During the TBS or sham treatment, the TMS coil over Fp1 will be fixed by a holder on the coil's handle during the treatment. We will pause to adjust the position if there is any movement of the coil or head according to the participant's feedback.

TBS Pattern

The cTBS will be applied to reduce activation of the OFC circuit. TBS sessions will be carried out with a hand-held figure-of-eight coil with the size of 90 mm diameter of one half of the "8" shape (B9076, Yiruide Co., Wuhan, China), attached to a YRD CCY-I stimulator (Yiruide Co., Wuhan, China). Following a 10-min rest after memory retrieval, participants either in the MA VR scene + TBS group ($n = 15$) or in the MA VR scene + sham TBS group ($n = 15$) or in the neutral VR scene + TBS group ($n = 15$) will receive two TBS sessions within 1 week. In each session, all participants will receive two 1,800-pulse trains of cTBS in 5 min (three pulses are given at 50 Hz as one burst; a burst will be given every 200 s as 5 Hz; one train for 120s, containing 1,800 pulses) with a pulse intensity of 80% of RMT following Hanlon et al. (62)'s suggestion. A 60-s break will give to participants after the first train (1,800 pulses). The choice of TBS intensity will consider the participants' real-time feedback and health condition to TMS stimuli. If a participant reported unbearable discomfort with TBS stimulation, we will turn down the intensity gradually until acceptable. If a participant still reported unbearable discomfort when the stimulation intensity was lower than 60% of the RMT, this participant will withdraw from the experiment. These parameters have been applied by previous studies (62) and proposed in safety guidelines (63).

Intensity Identification

The RMT is suggested as the minimal TMS intensity required to elicit motor evoked potentials (MEPs). It will be identified by flexion/extension movements of any finger, especially the index and little finger, in at least 5 of 10 consecutive MEPs trials (32). A single TMS session will be conducted by a figure-of-eight TMS coil following previous suggestions (64), with a gradual increase (5% each time) from 40% of median output intensity up to an intensity which could induce slight but significant finger movement. The coil will be applied over a suggested "finger motor cortex," with a TMS-matched elastic cap. This location was examined about approximately 8–11 cm lateral and 0–4 cm anterior to the cranial vertex (65). Thus, the TMS provider should concern with both cap-provided "marker" and information about a relative position, to find the "hotspots" accurately.

Sham TBS Protocol

The sham TBS treatment will be conducted with identical conditions of active TBS using a sham TBS coil. The sham coil has no difference in shape and appearance to that of the active coil except for an additional black coil sheath for reduction of the diffusion of magnetic fields. It delivers stimulation over only scalp skin and superficial muscles without proposed physiological modulation effects on the cortex (66).

Outcome Measures

Primary Outcome Measure

We will evaluate the short-term effects of Retrieval-TBS treatment in the reduction of cue-induced drug craving and cue reactivity by comparing EEG in VR scene between baseline (T0) and post-test (T3).

EEG will be recorded by a portable EEG system (Muse by Interaxon Inc.) during each VR session (3 min/scene × 1 MA-related VR scene and 1 neutral-related VR scene = 6 min) at T0 and T3, respectively. Each patient will wear an EEG headset before entering the VR scenes. Four channels (refer to EEG 10-20 system: FP1, FP2, TP9, TP10) and an original reference (FPz) will be retained to measure the brainwave spectrum including delta, theta, alpha, beta and gamma (with a sample rate of 256 Hz and 12 bit resolution), frequency bands between 45 and 60 Hz were omitted because muse hardware applied notch filters at 50 and 60 Hz to reduce environmental noise (67). According to a previous study, there was a significant difference between drug-cue and neutral-cue-induced EEG activities (68). In terms of drug-cue related memory, the frontal theta activity used as a feedback signal in adaptive regulation was highlighted for memory updating (69), which has been suggested as an indicator of the enhanced binding of incoming interconnected information in memory formation (70), while the beta activity which reflects a memory promoting state (70) indicated the level of memory integration in reconsolidation (71). Since the wearable devices available in VR have been applied to classify emotional states (72), we plan to use wearable EEG combined with VR scenes to observe the brain activity associated with memory in the current study. The average power in EEG frequency bands (i.e., $\delta = 1$–4 Hz, $\theta = 4$–8 Hz, $\alpha = 8$–13 Hz, $\beta = 13$–30 Hz, $\gamma = 30$–50 Hz) are real-time computed in hardware and sent alongside an indicator of data quality from each sensor. The Muse manufacturer provided on-device computed FFTs (https://sites.google.com/a/interaxon.ca/muse-developer-site/museio) were used to estimate the spectral power density (μV2/Hz) for frontal electrodes in each frequency band in this study. EEG spontaneous measures at the frontal sites were calculated, as shown in **Figure 2**, by 1 min post-dark data minus 1 min pre-dark data in each frequency band in each VR scene. We used state-related EEG to calculate the

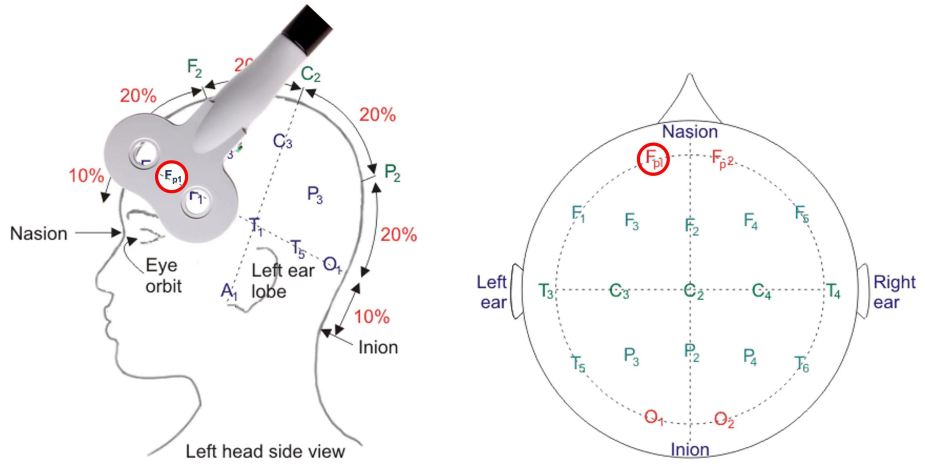

FIGURE 3 | The stimulation coil targeting Fp1 on EEG International 10–20 system positioning.

EEG activities for drug-related craving state in VR, because cue-induced craving is related to a tonic, slowly changing craving state and Muse is a portable device that may not stably acquire EEG activities during walking in VR scene. Previous studies have used "state-related EEG" to compare different EEG activities in different state (56, 72, 73). Because of the non-normal distribution, power density value and ratios were log-normalized. For statistical tests, a two-tailed alpha of 0.05 was used unless explicitly stated otherwise.

Secondary Outcome Measures

The secondary outcome will focus on the long-term effects of repetitive treatments on drug-cue-induced response. Evaluations introduced in primary outcome will also be collected in the follow-up test (T4). Furthermore, self-reported craving in VAS as a subjective indicator for cue-induced drug craving, physiological parameter (cue-induced heart rate) and possible co-variables corresponding to substance-taking history, emotional and mental state will be measured with the clinical diagnosis and psychological questionnaires at baseline (T0), post-test (T3) and follow-up test (T4) respectively.

VAS embedded in VR scenes is a 100-point visual analog scale ranging from 0 (no craving) to 100 (high craving) for self-reported craving. Each patient will be directed to evaluate their current craving at a black screen on one wall of a virtual room. They will be guided to focus on their momentary feeling to make an assessment. The VAS points at baseline (T0) will be compared with the post-test after the last treatment (T3) to identify an expected reduction in self-evaluated craving. The median, range, average and standard deviation of VAS will be calculated for analysis.

Electrocardiography (ECG) Given the association of MA with autonomic nervous system dysfunction (74) and the significant difference in heart rate between drug-cue and neutral-cue in the cue-induced craving paradigm (75), ECG (BIOPAC ECG module, with sampling rate of 1,000 Hz) will be recorded in this experiment as an indicator of physiological changes. In addition, changes in the heart rate interval can reflect abnormalities of autonomic nervous function (76). In addition, its activities are related to executive functions such as working memory, attention maintenance, and response inhibition involved in prefrontal cortex activities (77). In MA studies, it shows significantly reduced heart rate variability in MA populations (76), and the difference between drug-cue and neutral-cue is significantly associated with subjective cravings (78). Therefore, ECG will be recorded at the same time with EEG.

Anxiety as a specific unpleasant emotional state has been observed as a common psychiatric comorbidity in addicts (79). Each patient will be required to complete the Self-Rating Anxiety Scale (SAS) at T0, T3 and T4 (80). The questionnaire consists of 20 items rated on a 1-4 points scale, with a total score ranging from 20 (mild anxiety) to 80 (severe anxiety). The SAS has adequate internal consistency alpha coefficients ($\alpha > 0.7$). It is a widely used measurement of anxiety levels both in research and in clinical practices.

Depression is another common emotional state exhibited following intense drug craving (79). It will be assessed at T0, T3 and T4 with Self-Rating Depression Scale (SDS) (81). The questionnaire consists of 20 items rated on a 1-4 points scale, with a total score ranging from 20 (mild depression) to 80 (severe depression). The SDS has satisfactory alpha coefficients ($\alpha > 0.7$) and it has been implemented widely in clinic trials.

Mood State will be evaluated at T0, T3 and T4 with the Profile of Mood States -short form (POMS-SF) (82). The self-reported scale includes 40-items to identify the extent of feeling in respective mood state. The POMS-SF is indicated for current emotional state on a 5-point scale (1 = "very slightly or not at all" to 5 = "extremely"). It is widely used for clinical practice

in China (83) and its accessibility and consistent reliability coefficients have been identified among Chinese (with *Cronbach's* $\alpha > 0.7$).

Participant Timeline

All participants will be introduced to follow the schedule of baseline phase, treatment sessions and follow-up test. All patients passing the screening process will enter the treatment procedure. Participants will be grouped into A, B or C to receive MA-VR retrieval combined active TBS (MA VR-active TBS) or MA-VR retrieval combined sham TBS (MA VR-sham TBS) or neutral-VR retrieval combined active TBS (neutral VR-active TBS), respectively. The treatment includes two TMS intervention sessions within 1 week. Each session takes about 30 to 40 min including preparation time, VR retrieval of 3 min, relaxation of 10 min and continuous TBS of 5 min. The post-test will be conducted 1 to 4 days after the last session and the follow-up test will be taken over at least 1 month later. The timeline for participants in this trial is illustrated in **Figure 2**.

Sample Size

According to Hanlon et al. (28) study, 25 cocaine users either receiving active- or sham- pre/post TBS treatment showed a significant difference in the reduction of cue craving ($F_{1,\,96} = 5.65, P = 0.02$). The effect size ($f = 0.2496$) calculated by formula $r^2 = \frac{df1^*F}{df1^*F + df2}, f = \sqrt{\frac{r^2}{1-r^2}}$, the 3 (between factor: MA VR-active TBS vs. MA VR-sham TBS vs. neutral VR-active TBS) × 4 (within factor: four repetitive tests) design of the current protocol, the proposed alpha error ($\alpha = 0.05$) and power ($\beta = 0.95$) will be used as the parameters for a prior sample size calculation (in G.Power 3.1). The required sample size is 45 in terms of repeated measures ANOVA with within × between interaction effect.

Data Collection and Statistical Methods

The screener will ensure the inclusion and exclusion criteria and collect basic characteristic data before randomization. The outcome evaluators will play an important role in measurements of the primary and secondary outcomes. The data of all participants will be stored in documents and kept in locked boxes by the main investigator to protect personal information. Furthermore, the EEG data will be stored by the primary research on a locked computer with a password.

Data Preparation and Descriptive Statistics

After inspecting original data, identifying unusual cases, transforming and summarizing data-sets according to different types of variables: the mean, median, standard deviation, ranges and valid samples will be required at first, as well as the counts and percentages specific for categorical variables. Firstly, running SPSS 21.0 for basic check of validated data both based on the extent of treatment completion (>85%) and accepted level of missing/obscure/contaminated data (<10–20%). The missing data will be estimated via multiple imputations. Secondly, the distribution of data will be analyzed both by stem-and-leaf plot (SPSS 21.0), the actual data calculated for normality overlay a normal curve will be required to determine that to what extent it is a normal distribution (without significance at given alpha = 0.05). For a poor fitted normal curve, non-parametric inferential will be selected, while the standard or similar standard alloy will run the parametric inferential.

Inferential Statistics to Determine the Efficiency of Intervention

The statistical significance (sig) and effect size (ES) will be evaluated for treatment-effects determination either by paired *t*-test and repeated measures ANOVA test [two factors, test time (baseline vs. post-test) and treatment (MA VR scene + TBS vs. MA VR scene + sham TBS vs. neutral VR scene + TBS)] in parametric estimations or Friedman's chi-square and Kendall's W coefficients in non-parametric statistics. These differences between baseline and post-tests will be compared firstly between the three parallel groups for self-reported craving and neurophysiological measures (e.g., EEG and ECG).

Regression Analysis for Variables Prediction

A generalized linear modal (GLM) will be used for regression analysis of co-variation (e.g., emotion and mood state) and of the follow-up long-term effects by SPSS 21.0. The selected model with different statistics will be specified based on data characteristics such as the type of distribution. For example, a multiple linear regression model will be introduced according to stepwise regression to test whether there was any potential influencing factor among secondary indicators.

Monitoring

Definition of Adverse Events and Potential Risks

(1) referring to previous neuro-modulation studies, rare cases reported adverse effects of TMS, although some tolerable but uncomfortable feelings were reported by participants, such as mild itching, numbness or tingling, a slight headache, or head discomfort. However, these symptoms only existed for a short time and were relieved after stimulation ceased;

(2) according to existing cases and clinical practices, patients with following conditions are at higher risk to experience adverse sides in the treatment: (1) experiencing epileptic seizures or whose immediate family member has a history of epilepsy and mental illness; (2) having a history of brain diseases such as brain trauma, cerebral hemorrhage, cerebral infarction, or intracranial infection; (3) having intracranial metal or other foreign bodies;(4) having a pacemaker placed in the body.

Identification Method and Management System

(1) above potential risks will be considered within exclusion criteria to select adequate participants at the screening stage. These criteria will be re-confirmed again before the delivery of stimulation;

(2) individualized parameters for treatment: the intensity will be identified as RMT according to the individual threshold, and it will be adjusted (80–110% RMT) based on the tolerance of each patient;

(3) if there is persistent pain, intolerable, or the participant subjectively requests to withdraw, the treatment shall not be continued and concomitant care will be offered.

DISCUSSION

This protocol is proposed for a clinical translational study based on the theoretical framework of memory reconsolidation, using immersive VR for memory retrieval and TBS for neural modulation. The main purpose of this study is to investigate the effectiveness of neuromodulation during the time window of drug-related memory reconsolidation to reduce the craving of MA-dependent patients.

It has been proved in many clinical studies that the effect of pharmacological or behavioral intervention within the reconsolidation time window of drug-related memory is much better than that of intervention outside the reconsolidation window (84, 85). The enhancement of memory intervention during reconsolidation is due to the elevated lability during the post-retrieval period when the original memory trace is putatively re-written by pharmacological or behavioral interference (42). Non-invasive brain stimulation methods such as TMS and transcranial direct-current stimulation (tDCS), which have been applied to clinical treatment of drug addiction in recent years (62, 79), provide another therapeutic approach to intervening in the reconsolidation process. In addition, the TBS, a newly developed repetitive TMS pattern, is characterized by its short duration of application but long-term and better therapeutic effect (40, 86). We select the OFC as the target of TBS intervention because of the reciprocal connection between the OFC and the BLA which regulates the encoding and updating of the incentive salience of reward cues in associative memory (27, 87, 88). Evidence from pre-clinical studies shows that disrupting the activity of the OFC-BLA circuit during reward learning or memory retrieval results in impaired cue-induced reward seeking response (27) by interrupting the encoding or updating process of incentive salience (59, 89–92). Therefore, we postulate that TBS on the OFC may disrupt or weaken the functional connection between the OFC and the BLA during MA-related memory, thereby it can reduce the motivational and emotional value of drug cues and the craving response when an MA-dependent patient encounters cues.

Furthermore, the effect of reconsolidation-based interventions relies on the level of memory reactivating (93, 94). The more vivid the retrieved memory is, the better effect of intervention during the reconsolidation should be. A prominent advantage of VR in memory reactivation is the sense of presence generated by interactive, diverse cues presented in immersive and vivid scenarios (95, 96). MA-dependent patients are more likely to re-experience their drug-related episodic memories and generate MA cravings encountering drug-related cues and context in VR (95). Therefore, we propose that the incorporation of VR scenes in memory reactivation will further improve the effect of the follow-up TBS intervention.

Some caveats should be considered in the interpretation of findings from this study. First, the study will be conducted in compulsory drug rehabilitation centers where magnetic resonance imaging cannot be performed. Therefore, we will be unable to navigate precisely to deliver stimulation to a specific brain site nor to accurately evaluate the effect of the TBS intervention on the functional connectivity of the OFC-BLA circuit with the aid of fMRI. An alternative resolution is to assess the effect of TBS with EEG resting-state analysis before and after treatment (91, 97). In addition, our alternative plan is to locate the stimulation site by an EEG 10-20 cap (98). Although the location for delivery will be marked on the cap, it is difficult to remain stable across multiple treatment sessions. A portable neuro-navigation system for TMS is highly expected to improve future clinical practice.

The current study combines post-retrieval TMS intervention with VR to develop a new reconsolidation-based treatment for MUD patients. The findings of this study may provide the first and compelling evidence that TMS modulation after VR retrieval can reduce self-reported craving and drug-related cue reactivity. It will not only provide new ideas and insights for the clinical intervention of MUD, but also improve the understanding of the neural circuit mechanism of the reconsolidation-based intervention. Particularly, the TBS protocol, a highly effective stimulation pattern, may improve the efficiency of clinical intervention of TMS and promote the clinical application of therapeutic neuromodulation.

ETHICS STATEMENT

The Ethics Committee of the Institute of Psychology, Chinese Academy of Sciences has approved this protocol (H19007). The study will be carried out in accordance with the recommendations of this committee. All participants will sign an informed consent form (which will be gathered by the main investigator), providing their wish to do so, in accordance with the Declaration of Helsinki and with national and local regulations. The study is registered in the Chinese Clinical Trial Registry (www.chictr.org.cn) with ID: ChiCTR1900026902.

AUTHOR CONTRIBUTIONS

YW and YL conceived the study and designed the study protocol. YW wrote the primary manuscript and is responsible for formal analysis. XD, XC, and SQ contributed to the further development of the manuscript. YL and LW applied for funding. YL, XD, LW, and FJ provided supervision and resources. YW, YL, and LW prepared the ethical review application. XH is the leader of the investigation. XH, XD, QL, FeW, XY, and FaW are responsible for enrollment, data collection, intervention, and validation. SQ is responsible for data curation. All authors read and approved the final manuscript.

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Duration of the effectiveness of nicotine electronic cigarettes on smoking cessation and reduction: Systematic review and meta-analysis

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Background: The success of pharmacotherapies for smoking cessation in real-life remains limited, with a significant number of long-term relapses. Despite first promising results, the duration of the effectiveness of electronic cigarettes is still unknown. Our objective was to assess the duration of the effectiveness of electronic cigarettes on smoking cessation and reduction in daily smokers.

Methods: The databases EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and PUBMED were consulted until March 23, 2022. We selected only randomized controlled trials with daily adult smokers. The intervention was the nicotinic electronic cigarette *vs.* non-nicotine electronic cigarette or other validated pharmacotherapies (varenicline, bupropion and nicotine replacement therapy). The minimum duration of the intervention was 3 months, with a follow-up of at least 6 months. Two independent reviewers used the PRISMA guidelines**.** The primary endpoint was smoking cessation at the end of the intervention and follow-up periods confirmed by a reduction in expired CO $<$ 10 ppm. The reduction was defined as at least 50% of the initial consumption or by a decrease of daily mean cigarette consumption at the end of the intervention and follow-up periods.

Results: Abstinence at the end of the intervention and follow-up periods was significantly higher in the nicotine electronic cigarette group, compared to nicotine replacement therapy (NRT) [respectively: RR: 1.37 (CI 95%: 1.32–2.93) and RR: 1.49 (CI 95%: 1.14–1.95)] and to the non-nicotine electronic cigarette

condition [respectively: RR: 1.97 (CI 95%: 1.18–2.68) and RR: 1.66 (CI 95%: 1.01–2.73)]. With regard to smoking reduction, the electronic cigarette with nicotine is significantly more effective than NRT at the end of the intervention and follow-up periods [respectively RR: 1.48 (CI 95%: 1.04–2.10) and RR: 1.47 (CI 95%: 1.18–1.82)] and non-nicotine electronic cigarette in the long term [RR: 1.31 (CI 95%: 1.02–1.68)].

Conclusions: This meta-analysis shows the duration of the effectiveness of the nicotine electronic cigarette *vs.* non-nicotine electronic cigarette and NRT on smoking cessation and reduction. There are still uncertainties about the risks of its long-term use and its potential role as a gateway into smoking, particularly among young people.

KEYWORDS

electronic cigarettes (E-cigarettes), smoking cessation, smoking reduction, serious adverse effects, Electronic Nicotine Delivery Systems (ENDS)

Background

Each year, 8 million deaths are linked to tobacco use, including 1.2 million non-smokers involuntarily exposed to tobacco smoke (1). In addition, the morbidities caused by tobacco smoking have multiple harmful consequences and disrupt the psychological, familial and social equilibrium, with a high cost for society. It remains to be the world's leading cause of preventable death and a major economic challenge (2).

Smoking cessation is an important factor in reducing overall mortality. The earlier smokers quit, the greater the health benefits are. It is the decrease in smoking duration, rather than the decrease in the number of cigarettes smoked per day, that has the highest impact on health benefits (3).

For this purpose, several cessation aids exist. For pharmacotherapies, nicotine replacement therapy shows a 50–70% increase in the cessation rate. Compared to a placebo, varenicline doubles a smoker's chances of stopping, *and* it helps 50% more patients *than* nicotine patches and other substitutes (4). Finally, behavioral management and support associated with the various treatments increase the chances of smoking cessation by approximately 10–20% (4, 5). However, the success of these methods in real life remains limited, with a significant number of long-term relapses (6).

Developing strategies for refractory patients to make use of pharmacotherapies and for those who are not ready for complete abstinence is important. In this context, the tobacco harm reduction approach is on the rise. It involves achieving a safer alternative to tobacco consumption beyond complete smoking cessation (7). The overriding aim is to make it possible for people who are unable to stop smoking to consume nicotine in a less harmful form than tobacco (8, 9).

In this context, the nicotine electronic cigarette appeared in the 2000s (10). It is mainly composed of nicotine (optional), propylene glycol, glycerin and flavoring. It allows the inhalation of nicotine after heating the liquid. The principle is to produce an aerosol that imitates tobacco smoke by using a heating resistor that is part of the atomiser. Unlike a conventional cigarette, there is no combustion. Four generations of such devices have been marketed, and they have become increasingly effective in terms of autonomy, the distribution of nicotine and marketing (11–13).

Users generally have a good overall perception of electronic cigarettes and say that using them is a viable way of reducing or even stopping their tobacco consumption. In the context of stopping smoking, even though a majority of people try to quit alone, there has been an increase in the use of electronic cigarettes to help people stop smoking (14–16). Since emerging in the 2010s, the market for electronic cigarettes has stabilized despite the many controversies it has generated (17).

Despite a recent meta-analysis (18) clear recommendations do not exist because of the small number of studies that have been carried out and incomplete data on the effects of electronic cigarettes or their duration. Moreover, a recent study has questioned their effectiveness and noted a possible decrease in weaning since they were introduced into the European Union (19).

To update the actual knowledge on the efficacy of nicotine electronic cigarettes, we conducted a meta-analysis to answer questions about their duration of efficacy and safety.

Methods

We conducted a systematic review following the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines (20).

Objectives

- Main: To assess the duration of the effectiveness of nicotine electronic cigarettes on smoking cessation and reduction in daily smokers.
- Secondary: To investigate the long-term safety of nicotine electronic cigarettes.

Research method

The databases EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and PUBMED were consulted until march 23, 2022.

The following keywords/booleans were selected:

(1) for the device:

Mesh terms: *Electronic Nicotine Delivery Systems (ENDS), Electronic nicotine delivery device*

(2) for use:

Mesh terms: *Vaping, Electronic Cigarette Use, E-Cig Use*, *E-Cigarette Use*

(3) for quitting:

Mesh terms: *Smoking cessation, Quitting smoking, Tobacco cessation*

(4) for reduction:

Mesh terms: *Smoking reduction*

Non-Mesh terms: *Harm reduction*.

Eligibility criteria

Randomized controlled trials with daily adult smokers (> 10 cigarettes per day) were selected.

The study population includes smokers over 18 years of age without severe unstable diseases and current pregnancy or breastfeeding, with or without the intention of quitting. The intervention was the nicotine electronic cigarette *vs.* non-nicotine electronic cigarette or other validated pharmacotherapies (varenicline, bupropion and nicotine substitutes). Among the trials, those with a minimum of 3 months of intervention and a follow-up of at least 6 months were selected.

The primary endpoint was smoking cessation at the end of the intervention and follow-up period confirmed by a reduction in expired CO < 10 ppm. We used the most rigorous definition of abstinence when it was available. On the other hand, a reduction was defined as at least 50% of the initial consumption or by a decrease of daily mean cigarette consumption at the end of the intervention and follow-up period.

The secondary endpoint was the occurrence of the reported serious adverse effects of the nicotine electronic cigarette at the end of the follow-up period. Seriousness was defined as any effect leading to hospitalization (initial or prolonged), permanent disability, life-threatening situation or death (ICH Expert Working Group).

Trials not published in English or French were excluded.

Screening and data extraction

Studies measuring only effects on withdrawal syndrome were excluded. Two authors (AB, PV) independently screened the titles and abstracts of search hits to select studies of interest and reviewed the full texts. Disagreements were resolved by discussion between the authors. Information on methodology, participants and interventions, as well as the outcome measures, were collected by AB on an Excel spreadsheet and cross-checked by PV.

Risk of bias

The risk of bias was calculated using the new Cochrane RoB 2 Tool for randomized trials.

Quantitative analyses

The quantitative analyses were performed with the Revman® software version 5.3. The analyses were stratified for each outcome criterion by specific intervention and by comparator.

Once the results were pooled, we calculated the relative risk (RR) with a 95% confidence interval (CI 95%) in the number of participants in each group for each trial. We used the Mantel-Haenszel model to show the effect of the nicotine electronic cigarette as the binary variable and the inverse variance model for the continuous variable. The significance cut-off is $p < 0.05$.

The results from the binary variables were expressed as relative risk (RR) with a confidence interval (abstinence, reduction in consumption of > 50%, occurrence of serious adverse events). The results from the continuous variables (consumption per day) were expressed as a difference from the initial consumption +/- standard deviations in mean difference (MD).

In terms of effectiveness, a calculated relative risk higher than 1 was considered favorable. In terms of safety, a calculated relative risk lower than 1 was in favor of a less toxic effect of the nicotine electronic cigarette. The difference on average is significant for a positive value excluding 0.

The heterogeneity between studies was assessed using the I^2 statistic. If the I2 value was > 50%, the heterogeneity was

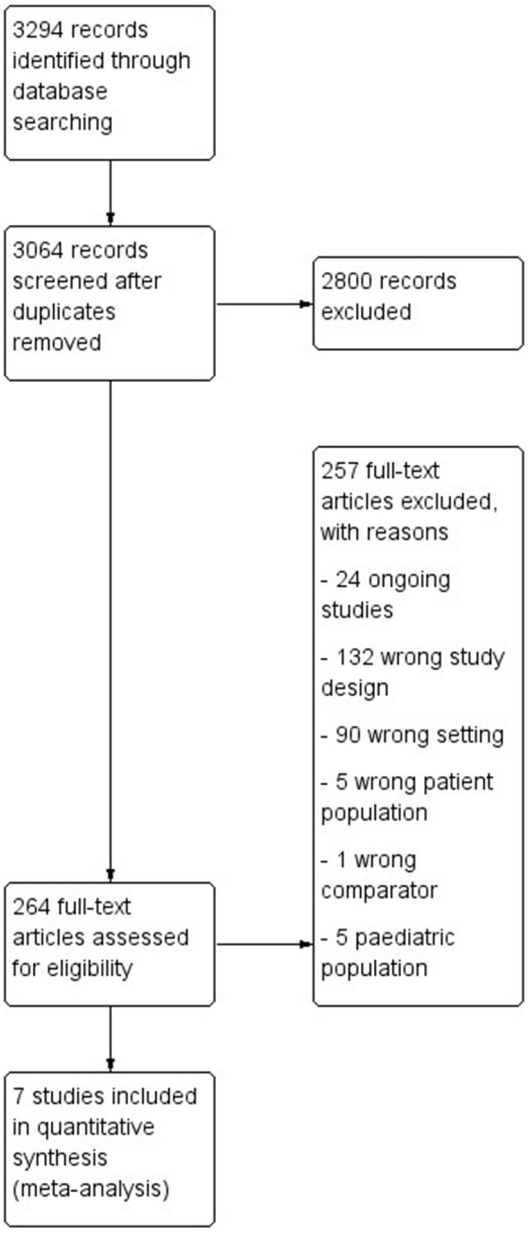

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

considered substantial; it was moderate for values between 25 and 50%; it was low for < 25%.

Results

We identified 3,294 articles using our search strategy. After the removal of duplicates and screening titles and abstracts, 264 full texts were assessed for eligibility, but 257 references were excluded mainly due to the lack of outcome data, their having inappropriate study designs or being ongoing studies (Figure 1).

Finally, 7 randomized controlled trials were included in the qualitative analysis (Table 1). They concern smokers with or without the desire to quit. The intervention is the use of the 1st (21, 22) or 2nd generation (23–27) nicotine electronic cigarette. The control group makes use of a patch and other nicotine substitutes, a non-nicotine electronic cigarette or both.

Risk of bias

Of all the studies, 4 of them use an open-label arm (Figure 2).

Intervention effect

The results of the analyses in the form of Forest Plot are listed for online-only supplements.

a) Smoking cessation

After statistical analysis, abstinence at the end of the intervention and follow-up period was significantly higher in the nicotine electronic cigarette group than in the non-nicotine electronic cigarette group, respectively: RR/ 1.97 [1.32, 2.93] and RR: 1.66 [CI 95%: 1.01–2.73] (Table 2). The nicotinic electronic cigarette is significantly more effective than nicotine replacement therapy, with a RR of 1.37 [CI 95%: 1.18–1.59] and 1.49 [CI 95%:1.14–1.95] at the end of the intervention and follow-up period, respectively (Table 2) (Additional file 1).

b) Smoking reduction

We found a significant reduction in consumption > 50% of the baseline with nicotine electronic cigarettes *vs.* nicotine replacement therapy at the end of the intervention and follow-up period [RR: 1.48 (CI 95%: 1.04–2.10) and RR: 1.47 (CI 95%: 1.18–1.82)]. Compared to the non-nicotine electronic cigarette, the nicotine electronic cigarette had a significant effect at the end of the follow-up period [RR: 1.31 (CI 95%: 1.02–1.68)]. The difference in mean daily consumption is significant in the 2 stages of analysis *vs.* non-nicotine electronic cigarettes and only at the end of the intervention *vs.* NRT (Table 2) (Additional file 1).

c) Serious adverse effects

In terms of safety, none of the included studies reports significantly higher serious adverse effects (SAEs) in the nicotine electronic cigarette group. After statistical analysis, compared to NRT, nicotine electronic cigarette has more frequent SAEs but no significant difference is shown with the non-nicotine electronic cigarette [RR: 1.53 (CI 95%: 1.02, 2.30) and RR: 1.18 (CI 95%: 0.65, 2.16)] (Additional file 1). No serious adverse

TABLE 1 Characteristics of included studies.

Authors	Study design	Duration of intervention: follow up (weeks)	Population (*N*)	Intervention (*N*)	Control (*N*)	Outcomes	Results
Caponnetto et al. ECLAT study (21) Italy	RCT 3 arms: 2 intervention groups and 1 control group	12: 52	300 smokers Not intend to quit	1st generation - E cig Arbi Group®, ad libitum use, 12 weeks at 7.2 mg (100) - E cig Arbi Group®, ad libitum use, 6 weeks 7.2 mg then 6 weeks 5.4 mg (100)	E cig 0 mg (100)	- Abstinence at 12months (since previous visit at 6 months, confirmed with CO < 7 ppm) - Reduction: CPD decrease ≥50% of initial - AE at each study visits	- Significant abstinence in nicotine group at week 12 and 52 vs E cig 0 mg - No statistical difference for smoking reduction - No serious AE reported
Cobb et al. (23)	RCT 4 arms: 2 intervention groups and 2 control group	24:36	520 smokers Not intend to quit	2nd generation - E cig EGO 8mg - E cig EGO 36 mg	- Cigarette substitute - - E cig 0 mg	- 7DPP and 28 day or more abstinence with CO < 10 ppm - Reduction: CPD decrease - AE	- Significantly more participants in the 36 mg/ml group than in the 0 mg/ml group are abstinent at 24 weeks - Significant decrease of CPD over times - Serious AE frequency similar across groups, not related to product use
Bullen et al. ASCEND study (22) New Zealand	RCT 3 arms: 2 intervention groups and 1 control group	12: 24	657 smokers Intend to quit	1st generation E cig 16 mg Elusion® (289)	- Nicotine patch 21 mg (295) - - E cig 0 mg (73)	- Continuous abstinence (≤ 5 cigarettes allowed) with CO < 10 ppm - Reduction: CPD decrease ≥50% of initial - AE	- No significant difference between nicotine e cig vs patches and vs 0 mg for abstinence - Significant decrease of CPD at 24 weeks - No serious AE classified as being related to product use
Eisenberg et al. (25) Canada	RCT 3 arms: 1 intervention group and 2 control groups	12: 52	376 smokers Intend to quit	2nd generation E cig 15 mg NJOY® (128)	- E cig 0 mg (127) - Counseling (121)	- 7 day PP abstinence - Continuous abstinence with CO < 10 ppm - Reduction: CPD decrease - AE at each study visits	- No significant differences in abstinence between nicotine and non-nicotine e-cigarettes groups at 12 weeks or 24 weeks - Significant decrease of CPD at 24 weeks - No serious AE

(Continued)

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TABLE 1 Continued

Authors	Study design	Duration of intervention: follow up (weeks)	Population (*N*)	Intervention (*N*)	Control (*N*)	Outcomes	Results
Hajek et al. (28) UK	RCT 2 arms: 1 intervention groups and 1 control group	12 (4 first weeks with behavioral support): 52	884 smokers Intend to quit	2nd generation E cig 18 mg Aspire® (438)	Nicotine replacement group: choice among the range of nicotine replacement products (patch, gum,...) (446)	- Continuous abstinence (≤ 5 cigarettes allowed) with CO < 8 ppm - AE at each study visits	- Significantly more abstinence in the E cig 18mg group than in the NRT group - No serious AE classified as being related to product use
Lee et al. (26) Korea	RCT 2 arms: 1 intervention group and 1 control group	12: 52	150 smokers Intend to quit	2nd generation E cig eGO-c ovale® 0,01 mg/mL (75)	Nicotine gum 2 mg (75)	- Continuous abstinence with CO < 10 ppm + 7 day PP abstinence at 12 and 24 weeks - Smoking reduction - AE	- No significant statistical difference at 12 and 24 weeks for abstinence - Smoking reduction was higher in the nicotine e cigarette group than NRT group - No serious AE reported
Lucchiari et al. (27) Italy	RCT 2 arms: 1 intervention group and 1 control group	12: 52	210 smokers Intend to quit	2nd generation E cig 8 mg (70)	- E cig 0 mg (70) - Counseling (70)	- Continuous abstinence with CO < 7 ppm - Reduction: CPD decrease - AE	- No significant statistical difference after 24 weeks for abstinence - Significant effect of group E cig 8 mg on CPD: after 24 weeks, participants in the nicotine e-cigarette group smoked fewer cigarettes than any other group. - No serious AE reported

RCT, randomized controlled trial; CPD, cigarettes per day; 7 day PP abstinence, 7 day point prevalence abstinence; AE, Adverse events.

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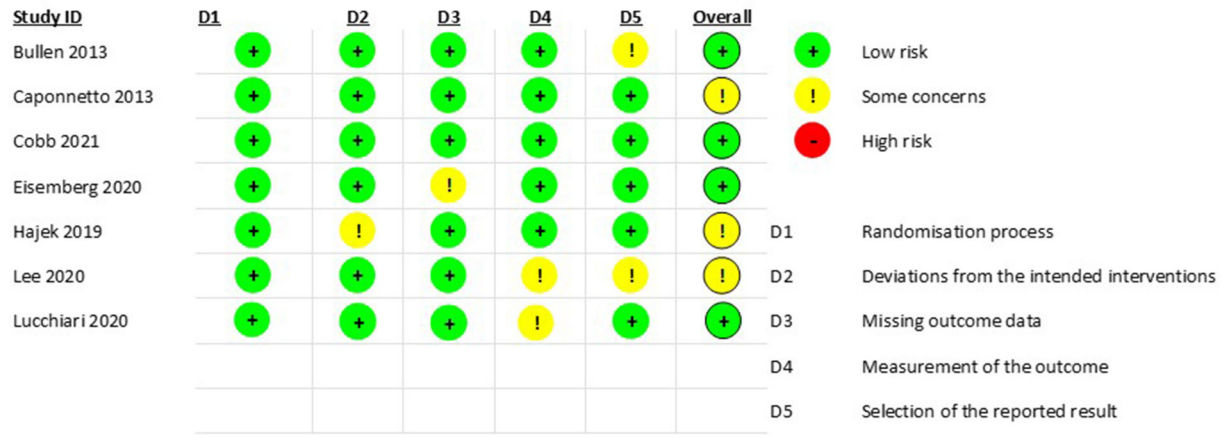

FIGURE 2
Risk of bias of included studies.

effects directly connected to the use of nicotine electronic cigarettes were reported.

Discussion

This meta-analysis, exploring the duration of nicotine electronic cigarette effect in the treatment of tobacco use disorders, finds a significant effect on abstinence in 1,618 smokers compared to nicotine replacement therapy and 1,447 smokers in the non-nicotine electronic cigarette condition. With regard to reduction in consumption, the nicotine electronic cigarette is significantly more effective than nicotine substitutes, at the end of the intervention and the follow-up period, and the non-nicotine electronic cigarette, at the end of the follow-up period. No serious long-term adverse effects attributable to the nicotine electronic cigarette were reported in the studies.

Some limits of our study should be acknowledged. First, the interpretation is limited by the small number of studies and patients included in the analysis overall. The data are incomplete for smoking reduction outcomes.

The experimental designs of the trials diverge. Their characteristics remain heterogeneous, particularly in their inclusion criteria. The co-morbidities and the presence of co-addictions differ between the ECLAT and ASCEND studies (21, 22). The secondary analysis of the Bullen study carried out by O'Brien in 2015 found no statistical difference in patients with or without mental illness (29). The majority of studies had a 52-weeks follow-up except for 2 studies of 24 and 36 weeks.

Also, one can bring out the argument that the randomized controlled studies were carried out with electronic cigarettes of different brands, dosages and generations, with an impact on withdrawal symptoms. The ASCEND and ECLAT studies use first-generation electronic cigarettes that distribute nicotine poorly and may have a negative impact on the results. The other studies use second generation devices that have a more efficient nicotine delivery (30). The novel cartridge Pods electronic cigarettes were not evaluated in our review, these new products are emerging in adolescent and young adults (31). They use a nicotine salt rather than freebase nicotine that allow an increase of nicotine concentration into the cartridge. For exemple, Juul products (59 mg nicotine/ml) have a pharmacokinetic profile close to the cigarettes. This pharmacokinetic profile can be dangerous for adolescents and young adults with a higher potential to generate regular use and create a dependence but also can be more efficient for smoking cessation (31, 32).

Similarly, the distribution and support offered to patients differ between these studies. The ECLAT study does not provide any support for withdrawal assistance: no motivational interviewing or cognitive therapy. The ASCEND study offered telephonic support and assistance, while the latest clinical trial in 2019 allowed participants to participate in multiple interviews and face-to-face sessions, which can increase the effect (33). Also, only the ECLAT study, unlike the other studies, included patients who did not intend to quit smoking (21).

Concerning outcome criteria, the definition of abstinence differs between studies. For reduction criteria, there is currently no consensus on a relevant verification method, making it a purely declarative value. The daily consumption was difficult to evaluate due to the lack of data expressed as a reference value. For smoking reduction, two studies (22, 24), excluded patients consuming < 5 cigarettes per day from the calculation, which biases the result.

Our meta-analysis is an update of a precedent publication from 2015 (34), which was the first study to analyse

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TABLE 2 Summary of findings.

Comparison	Abstinence		Reduction		Cigarette consumption		SAE
	End of intervention	Follow-up	End of intervention	Follow-up	End of intervention	Follow-up	Follow-up
E-cigarette vs. placebo	**RR: 1.97 [1.32, 2.93] I2: 33%**	**RR: 1.66 [1.01, 2.73] I2: 0%**	RR: 1.22 [0.78, 1.92] I2: NA	**RR: 1.31 [1.02, 1.68] I2: 0%**	**MD: 2.97[1.38, 4.57] I2: 89%**	**MD: 1.39 [0.30, 2.48] I2: 0%**	RR: 1.22 [0.54, 2.78] I2: 0%
E-cigarette vs. NRT	**RR: 1.37[1.18–1.59] I2: 53%**	**RR: 1.49 [1.14, 1.95] I2: 70%**	**RR: 1.48 [1.04, 2.10] I2: 51%**	**RR: 1.47 [1.18, 1.82] I2: 0%**	**MD: 1.69 [1.63-1.76] I2: 95%**	MD: 0.81 [0.00 – 1.61] I2: 84%	**RR: 1.53 [1.02, 2.30] I2:13%**

SAE, Serious adverse effects; RR, Risk ratio; NRT, Nicotine replacement therapy; MD, Mean difference/Risk Ratio (M-H, Fixed, 95% CI)/Mean Difference (IV, Fixed, 95% CI)/Bold: $p \leq 0.05$/.

the nicotine electronic cigarette effects by contrasting the end of the intervention and the end of follow-up periods with a threshold duration of 6 months. The last update of the Cochrane meta-analysis (18) reported the significant efficacy of the nicotine electronic cigarette *versus* non-nicotine electronic cigarette in terms of cessation and reduction. This effectiveness is determined at 6–12 months but not in the short-term. Moreover, the analyses include the measurement of physiological parameters but no longer include outcomes criteria that can assess the reduction in consumption. This outcome seems to us to be useful for evaluating the real effectiveness for smokers. Our quantitative analysis shows that the nicotine electronic cigarettes improve the smoking reduction and cessation at the end of the intervention and is stable over time. This is reassuring for smokers trying to quit or reduce smoking.

These conclusions remain consistent with the data from the cohorts of Polosa or Adriaens et al. in 2018 (35–37). We note, moreover, that it is also the frequency of its use that determines its effectiveness, as Berry suggests in 2019 (38). Nevertheless, many studies qualify that electronic cigarettes have no significant impact on abstinence. Khalkhoran and Glantz, in 2016 (39) go even further by talking about the negative effect of the electronic cigarette in terms of cessation and reduction, with rates 28% lower among electronic cigarette users. But this meta-analysis remains debatable because it is based on cross-sectional and cohort studies in addition to randomized clinical trials. It also includes longitudinal studies observing exclusive as well as dual uses of the electronic cigarette with tobacco products. The dual use represents a bias because it can be considered a failure in withdrawal. Indeed, this dual consumption reflects the persistent behavioral and social aspects of the addiction (40). It seems important to note that dual users must receive associated support (41). This support can range from minimal counseling to cognitive-behavioral therapy and online aid. The cost-effective advantage of the electronic cigarette together with support – *vs. the* substitutes – have been reported in a recent study (28).

With regard to the safety of the product, the analyses of this review are difficult to interpret and we cannot perform a detailed SAEs analysis. In the Caponneto and Lee studies, no serious adverse events were declared and in the Bullen study, no details was provided about the SAEs reported even if the authors declare that they are not directly connected to the use of nicotine electronic cigarettes. It is important to have more long-term and detailed data on nicotine electronic cigarette safety. In existing literature, adverse effects like coughing, irritation of the upper airways and nausea tend to diminish over time and during long-term exposure to electronic cigarettes (42). Overall, the electronic cigarette contains 6 constituents of concern, such as nicotine if it is present in high doses, carbonyls, volatile components (benzene, toluene), fine particles, metals

and bacteria (43). Exposure to these also appears to be greater when using particular flavors or depending on the voltage of the electronic cigarette (44, 45). Nevertheless, the toxic components are present in much smaller quantities than in conventional cigarettes. The nicotine electronic cigarette, therefore, seems to be safer (46–48), even if recent cases cast doubt on this last statement (49). A survey conducted in Illinois reports 53 cases of multiple lung damage (eosinophilic pneumopathy, diffuse alveolar hemorrhage, lipid pneumopathy) that were already described in 2012 (49). It was suspected that the causes were related to the use of electronic cigarettes. The 2019 update from the CDC (Center for Disease Control and Prevention) lists 2,172 cases of lung damage related to the electronic cigarette (EVALI: electronic cigarette vaping associated lung injury), including 42 deaths (50). The analyses highlight a potential relationship between vitamin E acetate, used as an additive in e-liquid with THC (tetrahydrocannabidiol), CBD (cannabidiol), and these lung lesions.

Finally, it seems particularly important to be observant of young people. The use of the electronic cigarette and the consumption of its additives tend to increase over the years, while proof of its safety is still lacking (51). Its use is therefore based more on curiosity about this trendy and customizable product than on its use for smoking cessation purposes (52). Three studies report a potential link between the initiation of electronic cigarette smoking in young non-smokers and subsequent active smoking (53).

Given the lack of consensus regarding the electronic cigarette, new approaches are being developed. Walker et al. have shown that a combination of nicotine patches and nicotine electronic cigarettes could improve the effectiveness of the electronic cigarette (54). A French study, the ECSmoke study (55) by Doctor Ivan Berlin, is underway and compares the nicotine electronic cigarette to varenicline. We should also mention the Swiss study, ESTxENDS (56), which compares the effectiveness of the electronic cigarette with support *vs.* support alone. Additionally, there are also other studies worth mentioning which explore the different effects of the electronic cigarette (57–59).

This meta-analysis shows the effectiveness of the nicotine electronic cigarette *vs.* non-nicotine electronic cigarette and NRT on smoking cessation and reduction at short-term and is globally stable over time without clear serious side effects. However, there have only been few studies carried out, which does not allow for an affirmation and recommendation of practice. Additional studies with long-term follow-up and new combined treatment seem necessary to confirm the effectiveness of the electronic cigarette. In addition, there are still uncertainties about the risks of its long-term use and its potential role as a gateway into smoking, particularly among young people.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

PV, AB, and CL-C contributed to the conception and design of the study, overviewed the conduct of the project, participated in the interpretation of the data, and critical revision of the manuscript. ND contributed to conception of research equation and design of the study. SK, PD, PC, MB, and NJ contributed to interpretation of the data and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Supplementary material

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A virtual reality craving study in tobacco addiction: The role of non-pharmacological support in tobacco detox therapy

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Nicotine addiction is a widespread, worldwide epidemic, causing six million deaths per year. A large variety of treatments for smoking cessation are currently available, including Cytisine, which is a promising drug due to its low cost and high safety levels. Notwithstanding the important amount of research on tobacco addiction treatments, smoking remains one of the most difficult substance use disorders to treat, probably also due to the fact that pharmacological treatment often overlooks other maintaining factors in this addiction, such as sensory impact and cue reactivity. To address this gap in both treatment protocols and scientific literature, we propose a study protocol in which we will compare the effects of combining Cytisine with Nirdosh, a herbal tobacco substitute, to Cytisine only in two groups of patients (C + N and C) who will also undergo exposure to four different virtual reality settings that will assess the importance of environmental cues. We will further assess mood and craving in the two samples, and include a control group taken from the general population. We expect the C + N group to report a more positive mood and a lower sensitivity to tobacco-related environmental cues.

KEYWORDS

tobacco, virtual reality, craving, nicotine, addiction

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Introduction

The tobacco epidemic is a major threat to human health and economic development. With one billion smokers in the world and six million deaths per year (1), nicotine addiction is the most frequent substance use disorder (SUD) in the world. To date, several treatments for tobacco addiction (TA) are available, one of which is cytisine. Cytisine is considered to be the oldest medication for smoking cessation and has been used for this purpose in some Eastern/Central European and Central Asian countries for over 50 years (2, 3). Like Varenicline, it is a partial agonist of the nicotinic acetylchloline receptors (nAChRs) with a high affinity for the alpha-4 beta-2 nAChRs subtype, and its main action is to reduce withdrawal symptoms following smoking cessation (4, 5). Several sources points toward cytisine's efficacy and effectiveness; it's well tolerated when taken at the recommended dose, and adverse events reported in trials are typically non-serious and self-limiting gastrointestinal and sleep disturbances (6–8).

To date, we know that pharmacology therapy is not enough to counter smoking addiction. In several cases it is important to couple Cytisine detox therapy with other non-nicotinic treatments. Anti-smoking pharmacological medications address only the physical component of smoking (i.e., nicotine addiction), but they do not resolve smoking's psychological components (cognitive, craving, social and behavioral including handling, holding and puffing a cigarette) (9, 10).

Craving, in particular, has been described as "the most fundamental and difficult problem for smokers who are trying to quit" (11). Several studies have been aimed at explicating the nature of tobacco craving and the factors that determine it. Craving is still conceptualized as a withdrawal symptom in some scientific literature (12), but this conceptualization doesn't explain various phenomena related to smoking addiction, such as the fact that smokers can experience high levels of craving even when they are smoking freely and are clearly not in a state of withdrawal (13). Moreove1r, the same levels of craving can be higher after a short abstinence (14). More generally, several studies show that craving is largely determined by smoking-related cues (SRC) and expectations. SRC, such as the handling of cigarettes and exposure to smoking-related objects or contexts, can provoke powerful craving responses in smokers (15).

Cue reactivity (CR) is a hypersensitivity to stimuli and motivational situations (16). CR has a relevant role in addiction because it may increase craving and relapse risks, since subjects with a history of addiction are more sensitive to substance-correlated stimuli (17).

Cue reactivity is an evolutive phenotype, a biological characteristic of interaction with the environment. While a familiar space with many trigger stimuli could increase craving, an environment without trigger stimuli could on the contrary prevent relapse in tobacco addiction (18).

Virtual reality

Virtual reality (VR) is a methodological approach that allows to recreate a realistic ecological representation of a tobacco craving-inducing situation. This approach has been used in several studies of cue reactivity (CR) in TA, especially for tobacco craving (19, 20).

Smoking is reinforced by a variety of sensory experiences (taste, smoke etc.) (21).

As of yet, none of the U.S. FDA-approved smoking cessation medications are specifically designed to address the "sensory impact" smokers report as desirable, satisfying, and reinforcing to their smoking behavior (22, 23). Sensory impact includes factors such as throat scratch, heat or coolness in the upper and lower airways, flavor (24, 25), and various sensations on the tongue, nose, throat, windpipe, and chest (22, 26). Sensory impact as a factor affecting cessation outcomes is critical to consider because, while outcomes improve with the use of approved cessation medications as compared to no treatment, relapse rates among treated smokers are still estimated to be as high as 50% 1 year post-cessation (27, 28).

Currently, there are several study related to the use of e-cigs for quitting and harm reduction in TA treatment (29, 30). To date, however, there are no studies about cytisine treatment and VR exposure in scientific literature.

Cytisine

Cytisine is an alkaloid that is present in the *Cytisus laburnum*, a plant which is widespread in Central, Eastern and Southern Europe; this chemical has been used since the Sixties as a treatment for tobacco cessation.

As an active substance, cytisine is approved in Italy, but no pharmaceutical company produces it. It is, however, possible to find it in galenic form in virtually any pharmacy.

Cytisine is a partial agonist of the nicotinic receptors for acetylcholine, antagonizing both the nicotinic and the endogenous effects of acetylcholine (3, 5, 31, 32).

Many studies have shown that, in nicotine addiction, cytisine could, on one hand, only slightly increase the level of dopamine in the mesolimbic system (to about half the levels that nicotine induces). On the other hand, however, by limiting withdrawal symptoms cytisine could reduce the rapid spike in dopamine levels due to the rapid nicotine intake associated with a cigarette puff: indeed, cytisine is an excellent ligand of nicotinic receptors, presenting an affinity for the receptors $\alpha4\beta2$ that is seven times higher than nicotine's (33, 34).

Most studies on the pharmacokinetics of cytisine have been conducted in animals, with few human studies present in literature. The half-life of the drug is approximately 4.5 h and its elimination is mainly renal; a metabolization process does not take place, with 95% being eliminated through urine (35, 36).

Thanks to these characteristics, we can exclude any interactions with other drugs, as well as alterations of the pharmacokinetics in case of liver failure; on the other hand, there is a lack of studies on the pharmacokinetics of cytisine in patients with kidney failure.

Cytisine treatment is generally well tolerated. The most frequent adverse reactions are: changes in taste, dry mouth and throat, decreased appetite and, in rare cases, nausea. Headache and irritability have been observed in some patients on the first day of therapy. Among the side effects, no significant weight gain was found, but a significant increase in blood pressure values (just under 3 mmHg) was observed.

When taken at the recommended doses (1.5 to 9 mg/day for 25 days), cytisine is not associated with an increased risk of side effects compared to placebo, although gastrointestinal symptoms are more frequent (7, 37).

High doses can also cause dizziness and muscle weakness. All these effects pass quickly by reducing the dosage. Cytisine does not induce psychophysical alterations and therefore can also be taken by those who drive vehicles or operate machinery.

Since 2016, the Azienda Ospedaliera Universitari Integrata of Verona (AOUI) has been supplying 1.5 mg Cytisine capsules for the in-hospital treatment of patients with the aim of providing cost-effective support for the treatment of smoking, promoting therapeutic continuity even after discharge and reducing the risk of relapse.

The dosage of Cytisine used for this study is that by "(38)," visible in the table below. This protocol is based on the dosage recommended by the manufacturer, and starts with 1 tablet (1.5 mg) every 2 h (up to 6 tablets per day) on days 1 to 3, coupled with concurrent smoking reduction to avoid symptoms of nicotine overdose. The patient then continues with a dosage of up to 5 tablets per day (1 tablet every 2.5 h) from days 4 to 12. Smoking must be stopped on day 5. After that, the patient continues with 4 tablets per day (1 tablet every 3 h) from days 13–16, then proceeds with 3 tablets per day (1 tablet every 5 h) on days 17–20, followed by 1 to 2 tablets per day (1 tablet every 6–8 h) from the 21st to the 25th day, then the treatment is stopped. (39).

Nirdosh

Nirdosh is a cigarette tobacco substitute (tobacco and nicotine free), registered to the Italian Health Ministry (registration code 1349698/R) produced by Herborea SRL (Company code 169252) and designed to help subjects during smoking cessation.

Nirdosh is a herbal mixture composed by basil, turmeric, licorice, cinnamon, cloves, tendu, sprague, and guggul.

We have chosen Nirdosh because it is simple to find, it is nicotine and tobacco free, and a registered medical device.

The primary outcome of this study protocol is to evaluate tobacco craving in 3 groups of participants; the secondary outcome is to evaluate the impact of Nirdosh in TA treatment.

Exclusion criteria:

- Pregnancy
- Unstable angina
- Pheochromocytoma
- Malignant hypertension
- COPD
- Epilepsy
- Psychosis
- Anxiety and depression severe
- Illicit drugs and alcohol dependence

Inclusion criteria:

- Tobacco addiction
- 18–65 years old
- Informed consent signature
- Prescription of cytisine according to the indications for use listed below

Dosage schedule for treatment with cytisine.

The following dosage schedule will be proposed ((38); **Table 1**).

Cytisine and Nirdosh will be provide free of charge to the study's participants.

Procedure

Development and creation of virtual scenarios

We developed, created, and tested four virtual scenarios:

1. A cue-free tutorial scenario (VR tutorial), through which the subject can become familiar with the virtual reality instrumentation to learn how to move and explore each virtual environment.
2. A cue-free domestic entrance (neutral scenario, **Figure 1**).

TABLE 1 Graduated dosage schedule (38).

Days	N. cps/Die	Frequency of intake
1–3	6	1 cps every 2 h
4–12	5	1 cps every 2,5 h
13–16	4	1 cps every 3 h
17–20	3	1 cps every 4 h
21–25	2	1 cps every 6 h

cps, capsule.

FIGURE 1
Neutral scenario.

3. An empty tobacco store (Figure 2).
4. A tobacco store with cigarette packs (Figure 3).

The subjects will be able to move within the virtual environments, but they will not be able to interact with the objects, except in the tutorial scenario. To reduce the possible insurgence of cybersickness [headaches, nausea, vomiting, dizziness; (40)], the subjects will be able to explore the virtual environments not only with the teleportation mode through the controllers, but also with real steps, which will be faithfully reproduced thanks to a virtual positional tracking.

The VR hardware supply is composed by: HTC Vive PRO Full Kit with wireless adapter; PC-Gaming Intel Core i7-9700K - GeForce RTX 2070 8GB - 16GB DDR4 - 480GB SSD - Windows 10 - WiFi; 49" or 55" TV monitor.

Safety and hygiene measures

Due to the COVID-19 pandemic, we will guarantee safety and hygiene in the virtual setting through these procedures: wearing of surgical masks; hand cleaning with an alcohol-based hand sanitizer; usage of waterproof foam replacements on the HMD that will be sanitized easily; sanitization of all hardware devices after each use with alcohol-based products.

Recruitment

The selection of the sample will be based on the inclusion criteria. A total of 78 subjects will be recruited in the Addiction Medicine Unit (AMU). They will be divided in three subgroups composed by 26 subject each. First we will recruit a general population group, to which participants will be assigned regardless of whether they smoke or not (GA group); then, two groups of smokers comprising patients that access the AMU's antismoking center will be created by randomly assigning patients to a group which will follow a nicotine detoxification program with Cytisine plus Nyrdosh (C + N group), and a second group which will follow a Cytisine-only detoxification program (C group).

Experimental procedures

During the first session, all subjects will sign the informed consent and will be interviewed for the collection of anamnestic and smoking history details.

The GA group will be required to attend a one-hour single session, in which they will fill out the POMS and VAS will be exposed to the 4 virtual scenarios according to the following 8 virtual protocol steps (Figure 4):

1. Compilation of POMS and craving VAS.
2. Exposure to VR tutorial for 3 min.
3. Exposure to the neutral scenario for 3 min.
4. Compilation of craving VAS.
5. Exposure to the empty tobacco store for 3 min.
6. Compilation of craving VAS.
7. Exposure to the tobacco store with cigarette packs.
8. Compilation of POMS, craving VAS, Simulator Sickness Questionnaire (SSQ) and Presence questionnaire (PQ).

The GA group will follow a different procedure compared to C + N group and C group, but the virtual 8 steps will remain the same for all groups.

The C + N and C groups will be involved in the following steps. They will be required to attend four one-hour-and-a-half sessions structured as follows:

1. First psychological session: the psychologist will give the medical appointment to the patient at the end of the visit.

FIGURE 2
An empty tobacco store.

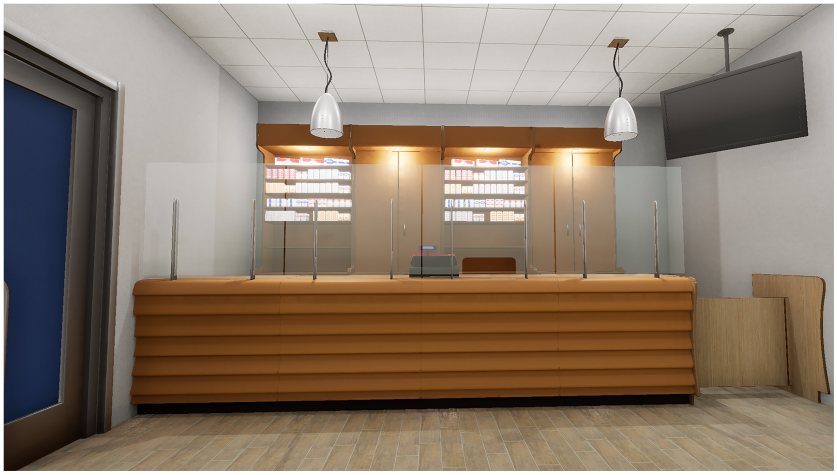

FIGURE 3
A tobacco store with cigarette packs.

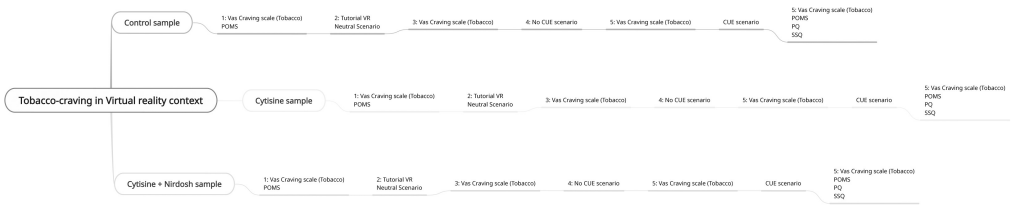

FIGURE 4
Study flow chart.

2. First medical appointment and exposure to the virtual protocol following the 8 steps above; in this step, the doctor will prescribe Cytisine and will explain how to take the drug (Table 1). Two packets of Nyrdosh will be given to the C + N group only.
3. Second medical visit and second exposure to the virtual protocol above, 7 days (± 2) after smoking cessation;
4. Third medical visit and third exposure to the virtual protocol above, 25 days (± 2) after ceasing smoking.

Questionnaires

In this protocol we will use several self-report questionnaires:

- Psychological assessment:
  - Personal information: gender, age, marital status, drug status, alcohol use/abuse, medical information.
  - Tobacco anamnesis: cigarette (daily), years of tobacco addiction, psychiatric comorbidities, other substances used, health information and previous detoxification programs attended.
  - Nicotine dependence levels will be measured by the Fagerstrom test for nicotine dependence (FTND), which is a widely used test for assessing physical nicotine dependence (41).
  - Beck Depression Inventory II (BDI-II): a widely used self-report questionnaire which measures depressive symptomatology (42). The BDI-II is composed by 21 items rating on a 4-point Likert scale (0–3 points per item), with a higher score for more severe symptoms (43, 44).
  - Beck Anxiety Inventory (BAI): a self- report scale that was developed by Beck et al. (45). The BAI is one of the most used and easy to understand. The questionnaire comprises 21 items which assess the cognitive, emotional, and physical dimensions of anxiety. Each item is measured *via* a 4-point Likert scale that ranges from "strongly disagree (0)" to "strongly agree (3)." The total score ranges 0–63 points. The Cronbach's α in the validation study was 0.93.
- Medical visit:
  - Profile of Mood State questionnaire (POMS): The POMS questionnaire comprises 65 items assessing the mood of the individual. A total mood disturbance (TMD) score is calculated by summing the totals for the five negative subscales, which are Tension, Depression, Fatigue, Confusion, and Anger, and then subtracting the positive subscale of Vigor. The POMS total score ranges from 0 to 60. High scores for tension, depression, anger, fatigue, confusion, and TMD reflect a negative mood state, and high scores of vigor reflect a positive mood state (46).
  - VAS craving scale: a single-item 10-point Likert visual analog scale (from 0 to 9) assessing craving. The question is "How badly do you feel like smoking right now?"
  - Simulator Sickness Questionnaire: The 16-item SSQ was used to assess participants' sickness levels before and after immersions in VR. Participants rated the severity of each symptom (e.g., dizziness, headache, sweating) on a 4-point Likert scale (0 – "None" to 3 – "Severe") (47).
  - Presence Questionnaire: The PQ is a subjective perception of the environment that the individual experiences and is made of a total of 19 questions based on "involvement," "immersion," "visual fidelity," and "interface quality." (48)

For the control sample, all questionnaires will be administered in only one appointment.

Statistical analysis

This protocol is a parallel group design.

Sample size:

The means for craving score, assumed to compute sample size, are reported in the following table.

	Baseline	After 7 days	After 1 month
Control	4	None	none
Cytisine	6	4.5	4.5
Cytisine + Nyrdosh	6	3.5	3.5

Assuming the above-mentioned means and a 0.5 correlation between repeated measures, 26 tobacco-addicted individuals allow achieving 80% power to detect significant differences with a two-sided alpha of 5%.

Statistical analyses

Significance of differences in craving score among the three groups will be evaluated by a repeated-measures ANOVA for mixed designs, where individuals will be the random effect, while the type of intervention and time (baseline/after 1 week/after 1 month) will be the fixed effects.

Estimated sample size for repeated-measures ANOVA and F test for between subjects:

Ho: delta = 0 versus Ha: delta! = 0.

Study parameters:

Alpha = 0.0500, power = 0.8000, and delta = 0.3600.

Estimated sample sizes: N = 78 N per group = 26.

Ethics Committee for Clinical Trials and approval code is 3624CESC.

Discussion

Tobacco addiction is a public health problem, causing six million deaths per year (1). There are several different pharmacological treatments for TA currently available, but Cytisine seems especially promising due to it having several advantageous characteristics: it is low-cost, it has rare pharmacological interactions, it has an easy drug management, and a good efficacy and safety (49). The low cost of cytisine is also its "*Achilles' heel*": the long registration procedures in Western European (EU) countries and in the USA restrict Cytisine's use to some Eastern EU countries. In most EU countries, and in Italy as well, there is the same paradoxical situation: the drug, albeit being registered in 4 EU countries (Poland, Bulgaria, Latvia and Lithuania) and 13 non-EU countries (Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldava, Russia, Serbia, Tajikistan, Turkmenistan, Uzbekistan, and Ukraine), could be prescribed as a galenic formulation by physicians, but only a few of them know its proprieties and few pharmacists agree to formulating it (8). There are several studies about tobacco craving and VR, and they report that nicotine cues could increase cigarette craving (12). But tobacco addiction is not only a pharmacological problem: there are other aspects related to this addiction (such as sensory impact) which are crucial in comprehensively treating addiction and preventing relapses in smoking cessation. Using Nirdosh will allow us to understand if a cigarette tobacco substitute could be advantageous in tobacco detoxification treatments. Concerning possible results, we expect the C + N group to present less environmental craving levels than the C (Cytisine-only) group. Using Nirdosh in addition to Cytisine therapy may lower the sensitivity of this group to tobacco CR. In addition, we expect that the C + N group will present lower POMS questionnaire scores than the C group. We hypothesize that using Nirdosh will also lower the levels of TMD scores, pointing to a more positive mood state in this sample. Since data quality is very important, we will also administer two questionnaires that address possible cybersickness effects and evaluate simulation quality. Indeed, the quality of the simulation could have an impact on the sense of craving and the mood of the subjects, so it is important to take into consideration.

There are several limitations to this research: using Nirdosh makes it impossible to measure Co^2 to observe tobacco abstinence, questionnaires are self-report measures and craving is measured using a self-report VAS scale.

Conclusion

Tobacco addiction is a complex addiction. With this protocol we want to study non-pharmacological effects on craving and mood state in subjects who want to quit smoking. There are several studies that analyze tobacco craving, mood states and VR separately, but, to the best of our knowledge, there are no studies that examine the use of tobacco substitutes to manage tobacco craving during smoking cessation treatment by also using VR to measure craving and mood states.

Author contributions

LZ, SCm, RG, MI, and FL were responsible for the study concept and design. RC, SM, FF, SCr, AC, ET, and IB drafted the manuscript. GV and RV were responsible for the study methodology. All authors critically reviewed the content and approved the final version of the manuscript for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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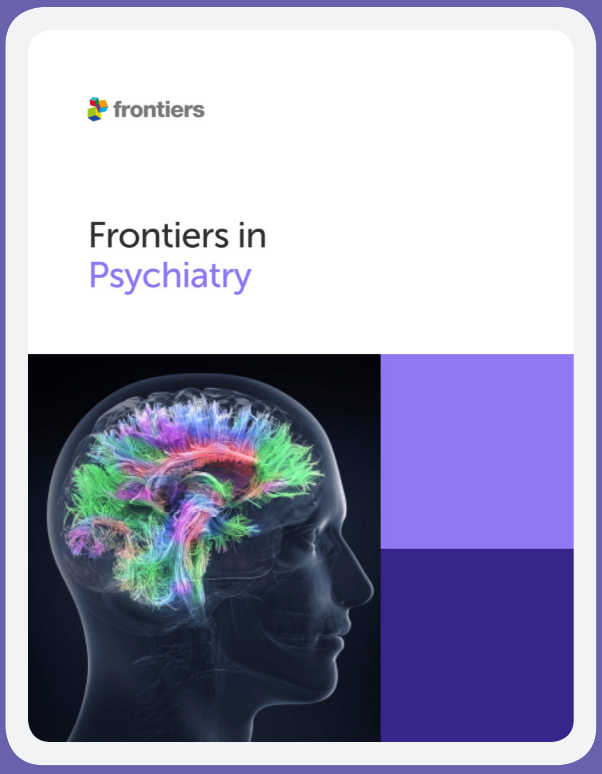

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